Anæsthesia

JOURNAL OF THE ASSOCIATION OF ANÆSTHETISTS
OF GREAT BRITAIN & IRELAND

VOLUME 15 · APRIL 1960 · NUMBER 2

'HIBITANE'

for disinfecting anaesthetic equipment

"Chlorhexidine is regarded as the most suitable disinfectant for anaesthetic equipment."

***Brit. J. Anaesth.* 1959, 31, 363.**

1. Immersion for half an hour in 1 in 1,000 aqueous solution achieves a bacteriologically safe disinfection of equipment such as airways, face masks, endotracheal tubes, etc.

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OF GREAT BRITAIN & IRELAND
LONDON

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THE ASSOCIATION OF ANÆSTHETISTS
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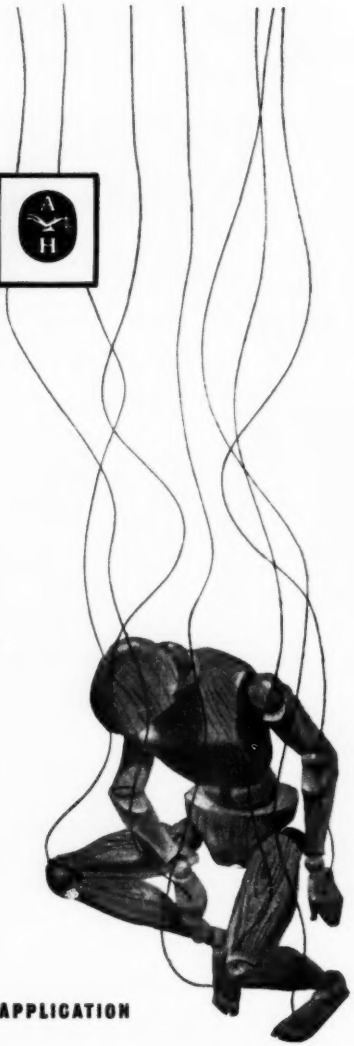

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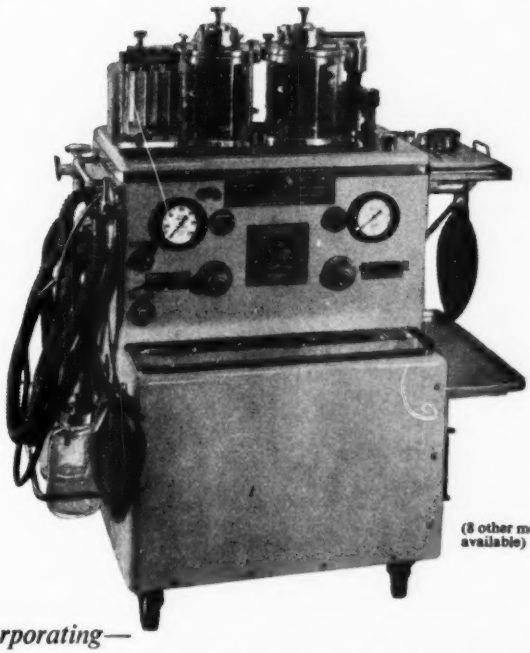

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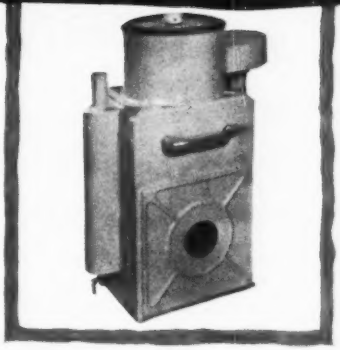

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EDITORIAL

The Council of The Association of Anæsthetists has for some time been considering the possibility of re-organising the Editorial Board of *Anæsthesia*.

The following alterations have now been made. Dr R. P. Shackleton becomes Chairman, Dr C. Langton Hewer continues as Editor, Dr Alfred Lee has been appointed Senior Assistant Editor and Dr Cyril Scurr, Junior Assistant Editor. Dr Blair Gould is leaving in October but has kindly consented to serve until this date. The Council would like to take this opportunity of thanking him for the sterling work which he has done for the Journal since the first number was published in 1946. Professor E. A. Pask has been appointed as additional member while Dr John Gillies continues in his capacity of Advisory Editor. The Board is completed by its two *ex officio* members, the President of the Association, Dr Ronald Jarman and the Hon. Secretary, Dr John Beard.

The panel of Advisers has also been enlarged and now consists of Professor W. D. M. Paton, Dr H. J. V. Morton and Dr P. Cliffe. Professor Pask and Dr Beard, who as already mentioned are on the Editorial Board, will also act as Advisers.

Mr Max Parrish will continue to act as Business Adviser.

With such a galaxy of talent it is hoped that *Anæsthesia* will steadily pursue an upward course - but we would like to make the fundamental observation that neither the Editorial Board nor the Advisers write the Journal. If it is to represent the specialty in a worthy way, contributions of the highest quality must continue to be received. May we suggest that many of our readers are well able to help us in this respect with the expenditure of a little effort ?

The control of consciousness

W. GREY WALTER, MA, ScD

Burden Neurological Institute
Bristol

The honour of delivering this lecture is all the greater because as a physiologist I must necessarily feel humble when I consider how little physiology has been able to aid your art and contribute to your knowledge. The introduction to British medicine of ether anæsthesia by John Snow over a century ago was an empirical innovation, and it is sad to consider that even to-day many of the most important advances in the control of consciousness have been due to bold guesswork and inspired commonsense rather than to a deliberate scientific development.

The modesty of the physiological contribution to anæsthesiology is not due to our lack of acquaintance with the art and action of anæsthetics; on the contrary, physiologists have long been in the habit of simplifying their problems by anæsthesia or mutilation or both, and this practice is embodied in the laws relating to experiments on animals. For the study of many organs in isolation this is no disadvantage, but when, during the last few years, we have begun to approach more closely the great ocean of problems around the continent of brain function, we have come to realise how treacherous and confusing can be a chart that is based on the assumption of placid seas and gentle currents.

As I have quoted elsewhere[8] physiologists are classically capable only of studying ' 'sciousness', since consciousness implies the joint action of many units and systems, isolation of which can only destroy their compound action. As particularly sobering examples of how far adrift the traditional methods may lead us, we may recall the classical teaching on spinal reflex action and the many 'facts' quoted in textbooks which are based on experiments with animals under chloralose anæsthesia. In my generation students were expected to appreciate the intricacies of spinal reflexes in decerebrate preparations,

The Second John Snow Memorial Lecture delivered at Stratford upon Avon on 22 October 1959

and our vision of the higher functions of the nervous system was a clumsy pastiche of these macabre creatures and the poetic imagery evoked by Sherrington's noble prose. We were never told, and rarely enquired, about how the literally rigid mechanics revealed in the bleeding carcases of our cats were supposed to be moulded into the exquisite living patterns of feline movement. We now know that by the blow on the guillotine, all the mechanisms of real importance in the modulation of muscle tone and action were sacrificed, not simplified. We are beginning to think now in terms of bias-modulation and anticipatory amplification, realising that our bodies are probably at least as intricate and well adapted to their functions as a rocket or a radar. Even when we withheld the knife, our syringes were often filled with drugs which satisfied our conscience and the law, but inflicted on the systems we now cherish disastrous and irreversible insults, resulting in a gross parody of normal states. It has been shown, for example, that administration of chloralose has an effect on afferent sensory transmission similar to transection of the spinal cord above the level of stimulation – the afferent signals are actually amplified and simplified[3].

We must accept that the very simplest account of the transactional mechanisms relating to sensation and consciousness must include at least six major interacting systems; the classical specific afferent highways, the devious paralemniscal by-ways passing through the brain-stem reticular formations, the pyramidal motor thoroughfares, the parapyramidal detours, the reticular traffic and route-control with its ascending and descending patrols and the central censorship channels whereby the central mechanisms block or promote access to themselves in varying circumstances. In the context of this lecture I cannot aim to discuss the absorbing details which make this new approach to consciousness so exciting to physiologists, but we can appreciate that, however devious the route, it must bring us closer to the problems that concern you in your profession.

Accepting then that the familiar classical sensory highroads, though essential, are not sufficient as a channel for conscious perception, we must consider how the control of consciousness is maintained and by extension, how it may be disturbed. If this assertion about the relative importance of the lemniscal and paralemniscal systems were based on experiments with rats, or even cats, we might be sceptical about its relevance to human experience, but it has been demonstrated that monkeys with bilateral destruction of the classical afferent tracts in the brainstem can still be awakened by sensory stimuli, while irreversible coma results from destruction of the mesencephalic reticular formation even when the classical pathways are intact[2]. More recently, as I shall show, studies of human beings have confirmed such findings,

though with many reservations peculiar to the human species. This situation is made even more dramatic by the clear and well corroborated report that electrical signs of sensory stimulation can be seen in the specific projection regions of the cerebral cortex when the animals are in deep coma after reticular lesion.

At this point I should interpolate a word of caution about the significance of electric signs of brain function. This science is still in its infancy and it would be easier – perhaps more profitable – to catalogue anomalies than to assert concordance. Elaborate and highly integrated function can occur without *apparent* change in the electrical activity of the brain and conversely, as in the above quoted observation – clear electric signs can be recorded with no evidence of behavioural change. Even at the purely physiological level there are bizarre discrepancies; for example prolonged and detailed experiments have shown that cats do not possess colour vision[5] yet electrical recordings from the cat's brain show clear differentiation of the cortical response to different colours of light[4]. The experimenter can sometimes tell better than the brain he is studying what sensations the organism could be experiencing – yet at other times he is quite out of touch. The clue, we must suppose, is in the word 'apparent' italicised above; our techniques are rudimentary, we cannot examine all parts of the brain all the time. Indeed, as we shall see from more intimate contacts with the depths and convolutions of human brains, our conviction grows that no human activity is quite alien to our enquiry, though much may remain obscured by distance and delicacy of detail.

Before embarking on the main theme of my discourse, I should like to summarise some of the main features of brain function which are affected by agents that influence consciousness. Very deep anæsthesia is not here our main concern – I understand that in any case such states are now rare and exceptional; the relaxation required for surgery need no longer depend on obliteration of the central control of muscle tone. The anæsthetic states produced by moderate doses of barbiturate derivatives are notable for three electrical effects – the primary specific responses evoked by sensory stimulation are almost unaffected, while the rhythm and distribution of *intrinsic* activity are dramatically modified, and the remote secondary and tertiary responses in association of 'silent' areas are quickly abolished.

It would be gratifying to be able to assert unequivocally what this means in terms of neurone function, but we are still debating vigorously how to interpret such observations. The balance of opinion is that this discriminatory action means that, at the neurone level, barbiturates act on the dendritic potential differences generated by internuncial neurones. Furthermore, the suppression of the non-specific remote effects of stimulation suggests that the primary

anatomical site of action of these compounds is in the deep central networks that provide, as it were, a significance filter for incoming signals. As I have emphasised elsewhere, this web of collateral channels involves several relay stations, and if we consider neural transmission as a probabilistic process, a cascade of relays must act as a probability multiplier. Suppose a given dose of anæsthetic reduces to one-half the probability of a signal traversing a single synaptic junction; this may not be of great consequence in a *parallel-connected* system – some signals will get through intact. But if the signal has to penetrate say ten such junctions *in series*, the likelihood of any signal emerging from the last relay will be one-half raised to the tenth power – more than one thousand to one against. Knowing as we do that the diffuse systems actually consist of such cascades, we have here a necessary factor to account for the dramatic efficacy of many neurotropic drugs in very small doses; whether this factor is sufficient to explain all their actions is another and equally challenging problem.

These concepts are, of course, rather academic and they are based mainly on experiments with domestic laboratory animals in highly artificial – though not any longer pathological – conditions. I am proposing shortly to present information derived from analogous studies of human beings but to provide, as it were, a vernacular bridge between the laboratory and the clinic, we may consider a social parable. Imagine a democratic state provided with the usual machinery of government, without an autocratic ruler, but determined by corporate evolution to survive as a social entity. If the environment of this community – the forces of nature and the neighbouring states – were entirely neutral or benign, survival would present no problem. But if there were – as indeed there is – a natural tendency to decay and some degree of foreign competition and hostility, the government would be bound to institute two complementary and co-operative organisations, one devoted to what we used to call propaganda and now euphemize as 'Information', the other to censorship. The scope and powers of such systems would depend on the urgency of the situation; in peace they would be latent and limited, in war supreme and absolute. Whatever their status at any particular epoch, these organisations would always have certain invariable features; they would be diffuse, non-specific and series-connected. Any item of approved significance, news or detail of policy, would pass through many hands and would be relayed by various, often devious and subtle means to all citizens. Contrariwise any irrelevant but disturbing rumour or event would similarly be checked and suffocated by progressive attenuation. Put yourself now in the position of a foreign power, anxious to control but not to destroy our supposed democracy. Admit that your ends are benevolent, to replace a 'corrupt' or obstin-

ate cabinet with one more amenable to your reason. Even a cursory study of social and political history shows us how this can best be done – by the infiltration of small doses of doubt and hesitation into the offices of propaganda and censorship. And how would you ascertain that your tactics were effective? By the clear and uncorrupted reproduction of news supplied to your agencies which would otherwise have been suppressed, and by the failure of the authorities to disseminate their version of crucial events and decisions. The State would have become a physiological preparation – or a patient ready for the healing knife.

If I may extend this parable one stage further, manœuvres such as I have outlined (which, of course, are familiar to the readers of Machiavelli and Hitler) are of trivial or transient theoretical interest when all that is concerned is the adjustment of a frontier line or the independence of a colony. Amputations and midwifery require skilful manipulations on your part, but it is in interference with the seat of Government – manipulation of brain function – that these issues become of vital importance. I am not referring so much to the anæsthetic management of neurosurgical problems – though this has great interest – but rather to the ways in which we are attempting, albeit clumsily, to influence conditions of brain function which we believe to be undesirable.

Not being a clinician myself the 'we' here is an editorial or social plural. The criteria of human excellence are perhaps less precise now than they ever were; our social tolerance is wide and our compassion deep and our sense of responsibility diffused. We are becoming reluctant to take or create life without pondering the issue, even when this may seem quite clear by the standards of our forebears. Social responsibility, we feel, extends indefinitely in all directions and we must all share a little of the glory of good deeds and the shame of evil ones. So, when my clinical colleagues, after deep thought and meticulous consultation, decide to interfere with the internal policy of a patient's brain, I am convinced that their purpose is one that we can all commend and that their means shall be the best that I can contrive for them. I can only apply the rule-of-thumb ethic – if this were I or one I loved, my attitude and my actions would be the same.

Such problems arose in this form only recently in human history, with the introduction about twenty years ago of the prefrontal leucotomy operation by Moniz. The general reality of the moral problem is illustrated by the award of the Nobel Prize to the innovator and the absolute prohibition of the operation by political authorities in the Vatican and the Kremlin. Such a division of opinion, cutting clean across the cleavage planes of party and history, religion and policy, may be far more ominous and more intractable than the more

open discords that fill our papers to-day. The institutions of the Holy Inquisition and the Siberian labour camp may seem to us far less humane and pardonable than attempts to heal the helpless and hopeless insane, ignorant though we may be of first or final causes. The human tragedy is not in the simple conflict between good and evil men, but in the remorseless struggles between those with unalterable convictions that their claims are just.

No one who participated in the early explorations of psychosurgery felt any conviction that this massive physical interference with cerebral function was right. Our only assurance was that in many cases, by our everyday criteria of wartime social tolerance, it seemed to work where other methods had failed or could not be applied. Certainly no physiologist, accepting the pragmatic sanction, could sit in judgment in the cause, for what had we contributed to the guidance of the psychiatrist or the surgeon? It is interesting that few object very strongly to efforts to make people change their minds, whether in missionary zeal or psychiatric healing, while attempts to change their brains arouse violent feelings. As Sargant[6] has shown, the boundaries between conversion, psychotherapy, conditioning, brainwashing and physical psychiatry are very hard to define and fluctuate from year to year and culture to culture and it is not for me to define the limits of ethical tolerance.

Physiologists have long been familiar with the mechanism and effects of conditioning and during the last few years have begun to appreciate also the functional relations of brain regions which had been obscured by the early methods; the combination of conditioning procedures with selective, localised, reversible cerebral destruction seems to offer at last a legitimate and rational approach to a physiological psychiatry.

The techniques which have been developed for this purpose derive from several sources. There are first the now familiar electronic procedures of amplifying and recording the electrical activity of the brain and other organs, electroencephalography or EEG, and polygraphy. Next is the application to human beings of the methods elaborated by the great Russian school of Pavlovian physiology, the establishment and manipulation of conditioned reflexes. Third is the development of surgical and stereotaxic means for inserting into chosen portions of the human brain, minute wire electrodes, so fine and so stable that they can be left in position without danger or discomfort for periods of weeks or even months. Last is the establishment of ways to use these electrodes, not only to record and analyse the electric signals of brain activity, but, in reverse, to stimulate, inhibit, suspend or obliterate cerebral functions associated with a particular patient's disorder or disability. A full account of the

details of these technical developments would require a monograph – we are concerned here more with their achievements and implications.

I should admit at once that, like all other investigators in this domain we have learned little about functional disturbances of mentality from conventional passive EEG records. When consciousness is severely impaired, of course, there are nearly always gross abnormalities in the EEG, but in the states of altered awareness and perception encountered in contemporary anæsthetic administration with relaxant drugs, the superficial EEG is scarcely outside the normal range. Similarly in the peculiar conditions of hypnosis, even when there are marked subjective and behavioural alterations, the intrinsic brain rhythms are almost unaffected. On the other hand, certain features of mentality *are* reflected in the characters of the EEG, and this relation becomes clearer as the conditions of investigation are made to approximate more closely to those of real active life[29].

When studies of the EEG are combined with registration of other physiological variables, particularly those associated with the autonomic nervous system, and this medley of information is collected during the establishment of a complex conditioned reflex, then the specific temperamental features are emphasised and their dynamic associations emerge.

This may be illustrated by reference to three subjects, one a normal young scientist, the other two being patients referred for neuropsychiatric investigation and treatment.

In our experiments with human conditioning, three types of stimuli are presented; a gentle warning tone of high or low pitch, a flashing light giving triplet or doublet flashes (these are neutral stimuli later to be conditional ones), and a painfully loud penalty sound which the subject can stop or avoid by moving a lever to the left when the low tone and doublet flash are presented, to the right following the high tone and triplet flash. The subjects have to discover this association for themselves – they are given no explicit instructions – but the penalty is disagreeable enough to provide a powerful incentive to succeed, and it evokes marked changes in the brain and autonomic nervous system; it is in effect the specific or unconditional stimulus. The warning tones and lights also usually produce changes in the EEG and autonomic behaviour particularly at first, and in the course of a conditioning experiment we, therefore, record some hundreds of such effects.

The results of these experiments are presented in four records, the EEG, the frequency analysis of this, a series of photographs of brain activity displayed in map form by the toposcope, and the record of somatic and autonomic variables. From these raw data computations are made and graphs drawn to show how the various factors change

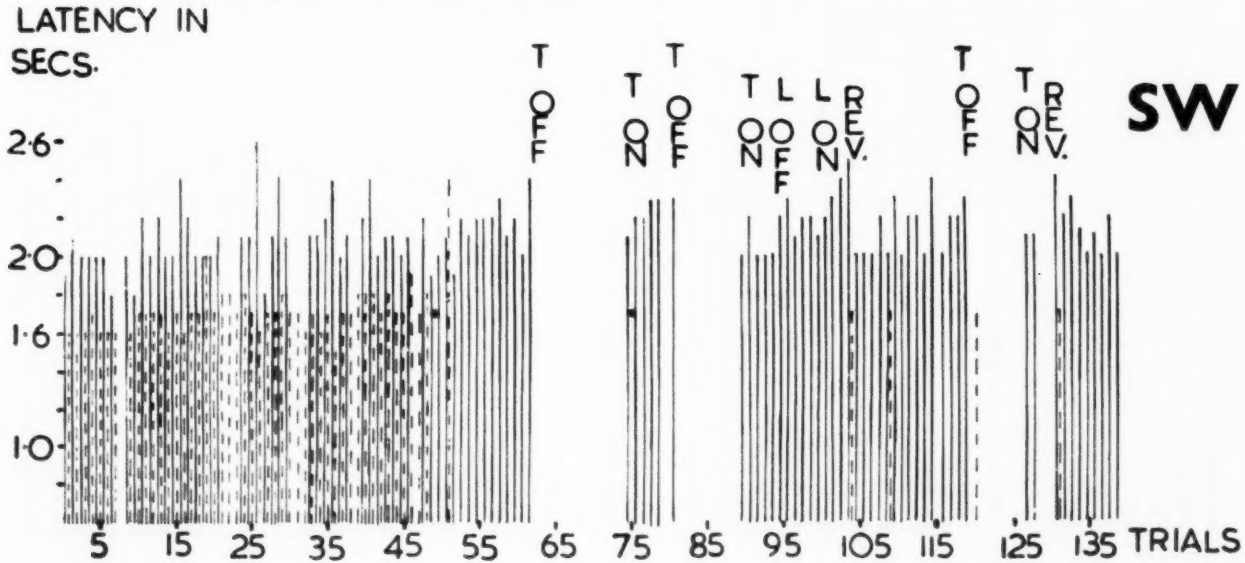
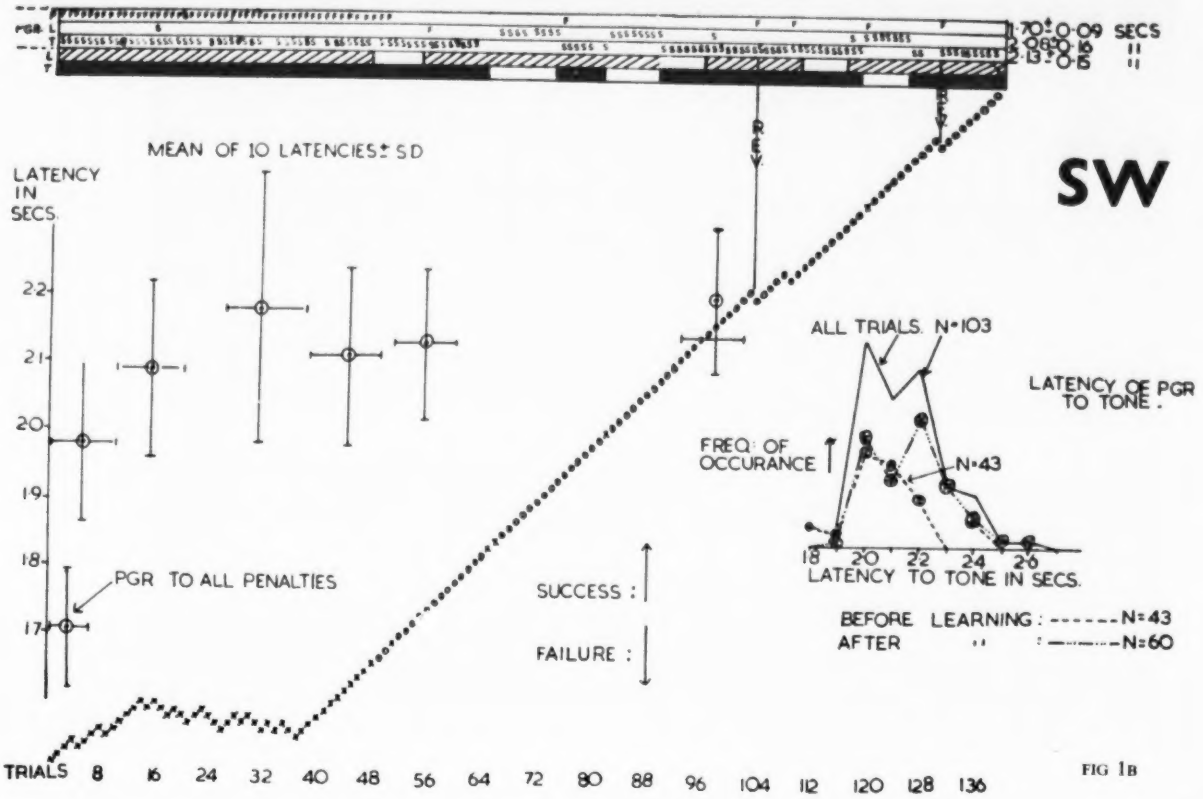


FIG. 1. (A) Histogram plot of GSR latencies during conditioning of a normal subject S.W. Number of trials are on the abscissa; latencies in seconds on the ordinate. Responses to unconditional penalty stimuli are dotted, those to conditional warning tones are solid lines. Note the consistent brevity of the unconditional as compared with the conditional latencies. (B) Conditioning curve and GSR latency distributions in subject S.W. There is no overlap between penalty and conditional latencies, but the scatter of the latter is greatest just before the appearance of consistently correct responses. Correct responses are plotted upward, incorrect downward. Defensive movements are indicated by crosses, anticipatory avoidance by circles.

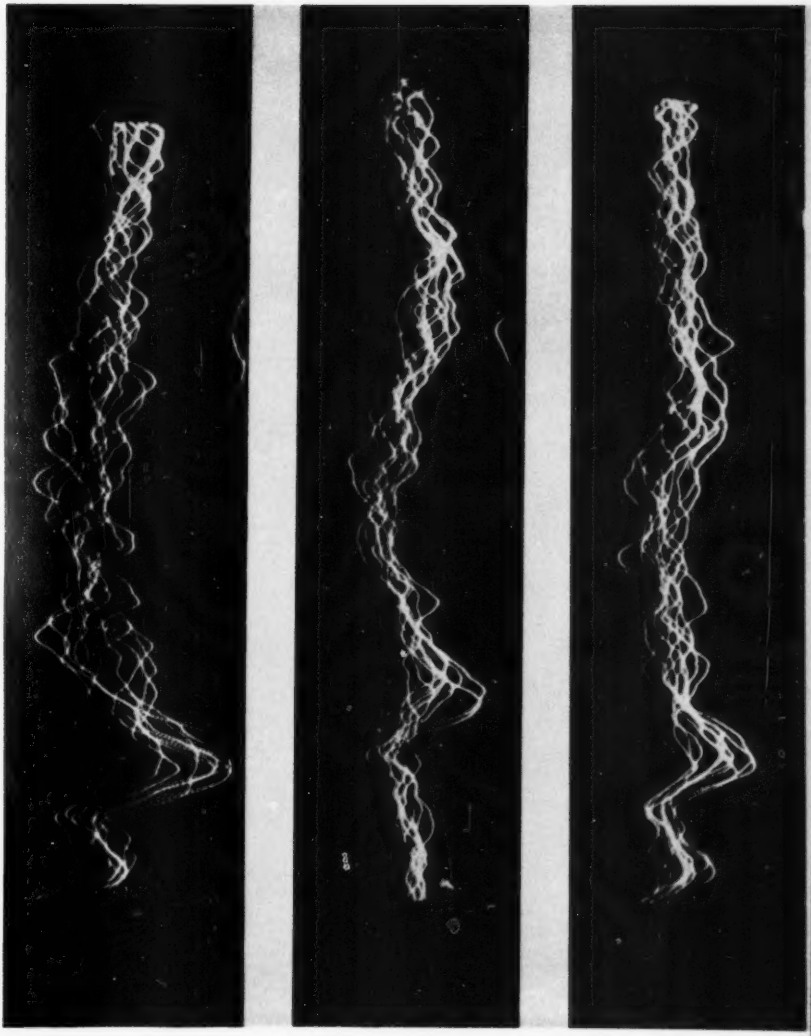


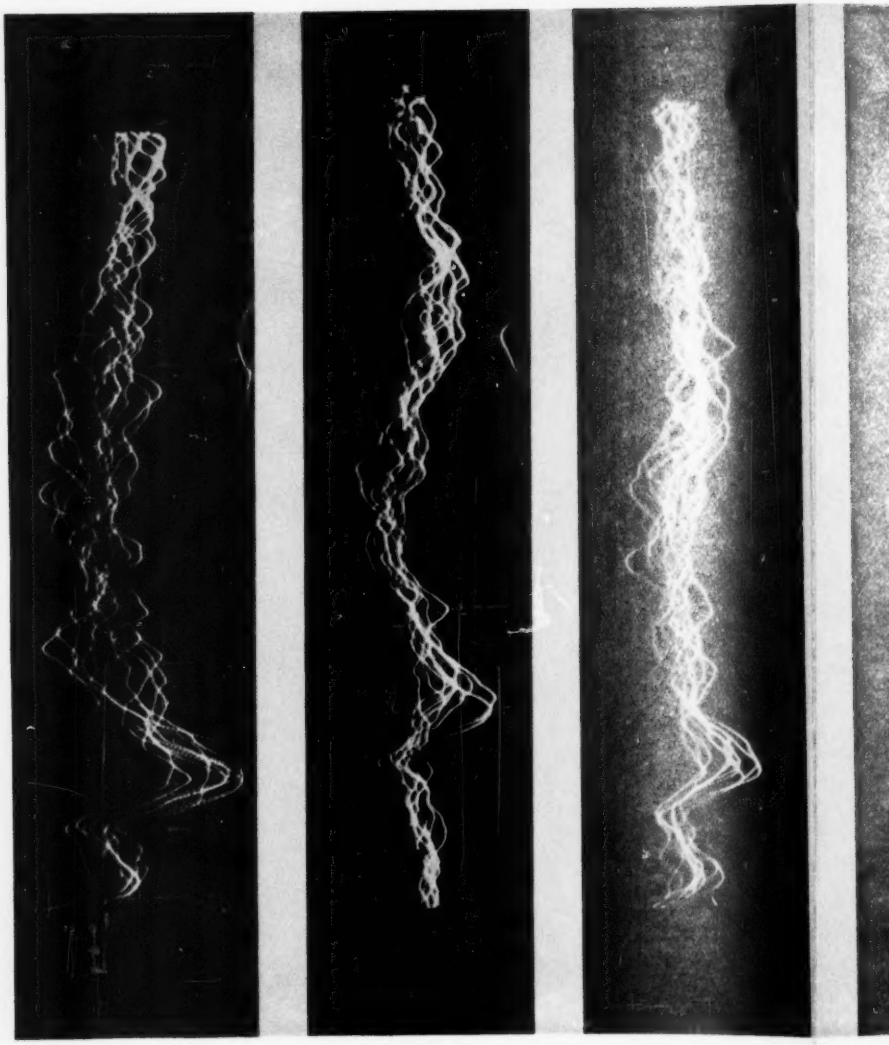
ANÆSTHESIA

FIG 1B

during the conditioning. The features I wish to refer to here relate first to the graph of conditioning (which indicates the success or failure of the subject to establish a novel relevant association), second to the change in autonomic responsiveness as indicated by measures of the latency of the psychogalvanic response or 'PGR' (that is the drop in the electrical resistance of the palm of the hand following stimulation) and thirdly the type and distribution of the electrical changes seen in the depths of the brain during the presentation of the Conditional (CS) and Unconditional Stimuli (UCS). In the first, normal subject, of course, the depths of the brain could not be investigated so I shall present only the learning curve and autonomic responses in his case. (FIG. 1).

In this subject (SW), an intelligent, self-confident young engineer of wide interests, the first responses were quite random and the learning curve remains horizontal, but at the 38th trial there appeared a series of ten correct defensive responses, a run of successes extremely unlikely to be due to chance. At this stage of successful defence the pulse rate, which had risen from 75 to 110 at the beginning of the experiment had fallen to 85 and the PGRs to the light (which were rare even at first) had disappeared, suggesting that the subject was being guided by the pitch of the warning tone rather than by the flicker pattern. Accordingly the flicker was omitted at the 48th trial, which evoked a correct defensive response, and at the next trial appeared the first correct anticipatory avoidance response to the tone followed by five further avoidance successes. The flicker CS was then re-presented with the tone which still served as a clue to correct defence. After a sequence of ten more successes, the *tone* was omitted and the next two responses, though correct, were not anticipatory, but after this, correct defensive anticipation was evoked regularly by the flicker patterns alone. When the tone was re-introduced, however, the response was made to this, the first CS, rather than to the light, and when the tone was again withdrawn there was a single failure to anticipate, but from then on only one error was made accompanied by a deep sigh and theta rhythm in the EEG. Altogether a hundred trials were needed to perfect this very simple response adaptation. The completeness and certainty of the response were tested by arbitrary reversal of the control rules; inevitably the response to the first trial under the new rules was wrong, but at the second the subject reversed his own procedure and made no mistakes, though the instrumental response time was almost doubled, from 0.8 to 1.5 seconds for the next few trials. The sudden reversal of rule not only provoked the inevitable unconditional PGR, but a pulse acceleration from 75 to 90, a series of gasping respirations, and a slight shortening of the conditional PGR latency to subsequent trials. Further reversals





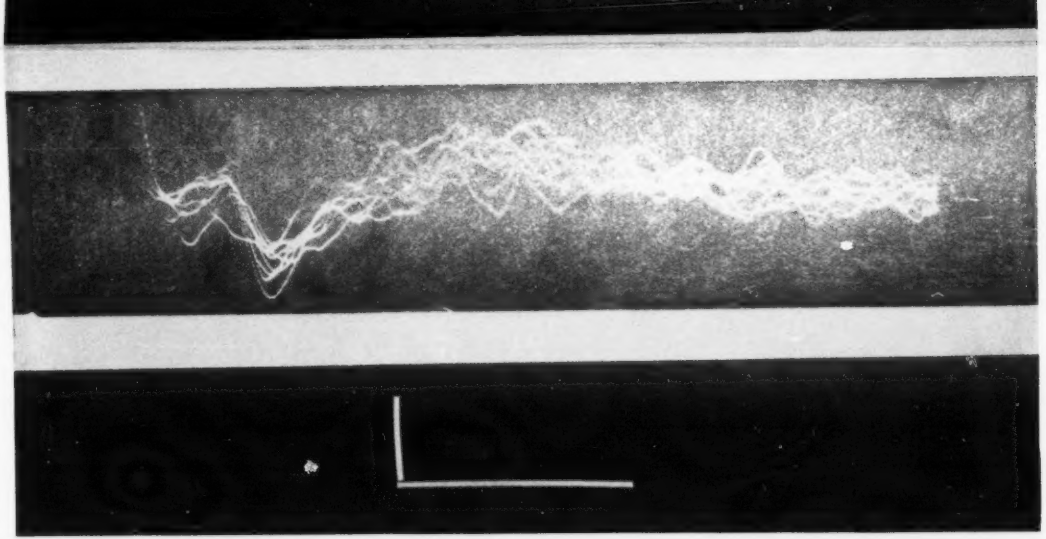


FIG. 3. Non-specific generalised electrical responses to visual and auditory stimuli within the frontal lobes of patient P.C. Superimposition of ten responses:

A Response to clicks at random intervals at electrode implanted in left lateral frontal cortex.

B Responses to flashes at random intervals at the same electrode. Note short latency and constancy of click responses contrasted with longer latency and habituation to visual stimulation. Similar non-specific responsiveness was found in many frontal regions of both hemispheres in this patient.

C Effect on responses to combined flash and click of distraction by conversation.

D Effect on combined responses of direction attention to the stimuli. Calibration: 100 microvolts, 100 milliseconds.

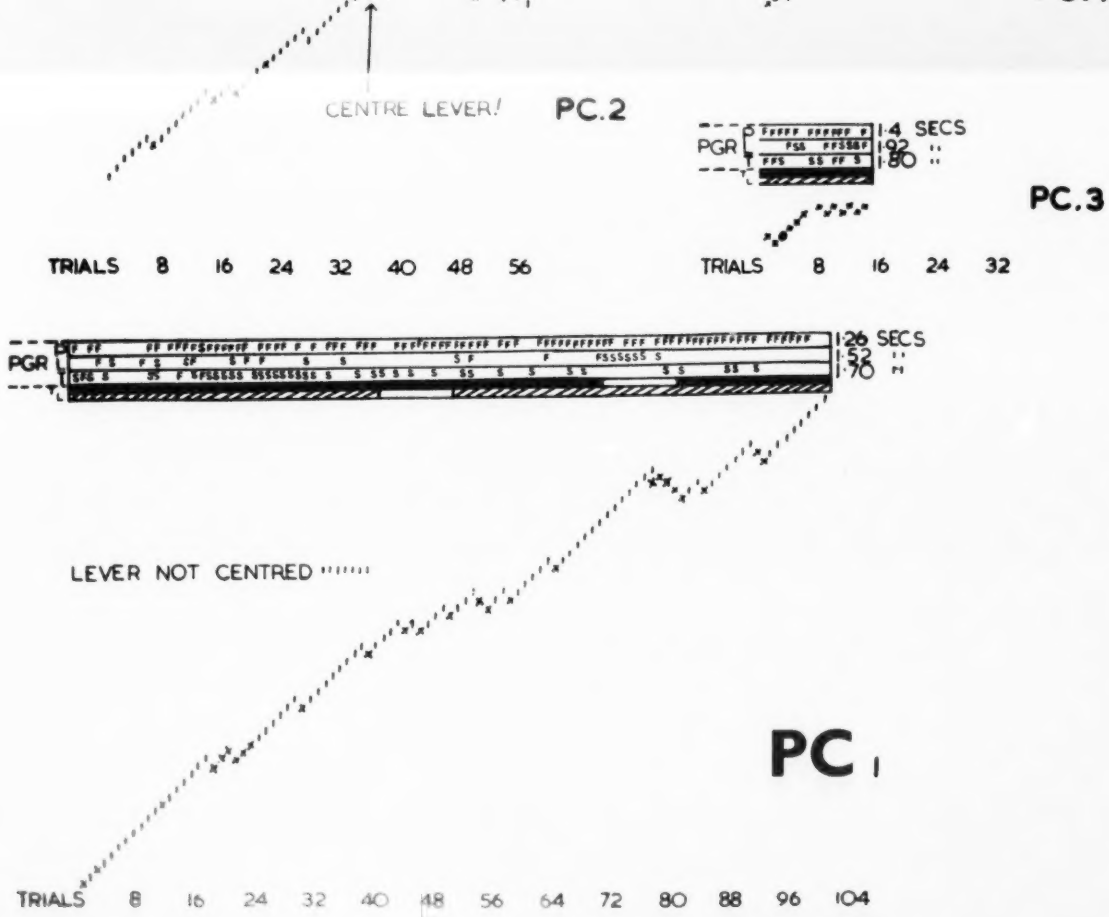

CENTRE LEVER!
PC.2
PGR
1·4 SECS
1·92 "
1·80 "
PC.3
TRIALS 8 16 24 32 40 48 56
TRIALS 8 16 24 32
PGR
1·26 SECS
1·52 "
1·78 "
LEVER NOT CENTRED
PC.1
TRIALS 8 16 24 32 40 48 56 64 72 80 88 96 104

FIG. 2(B)

FIG. 2(A)

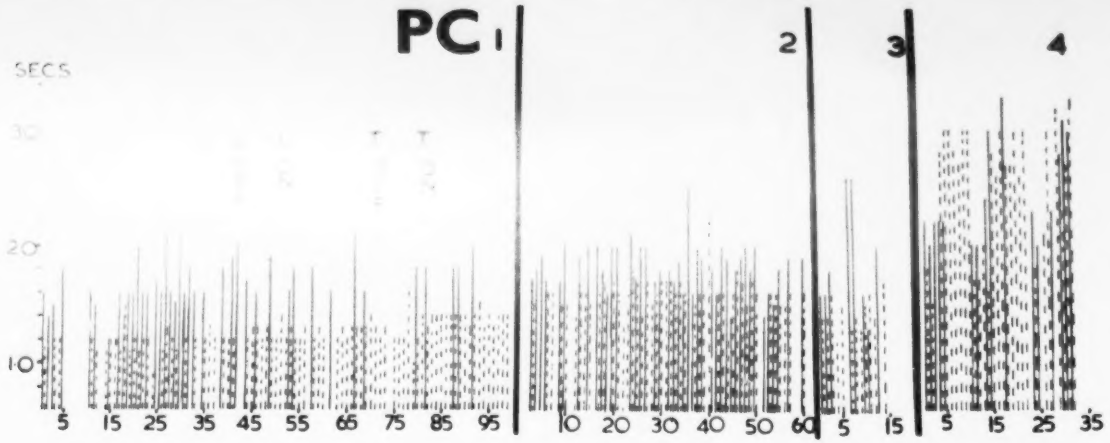
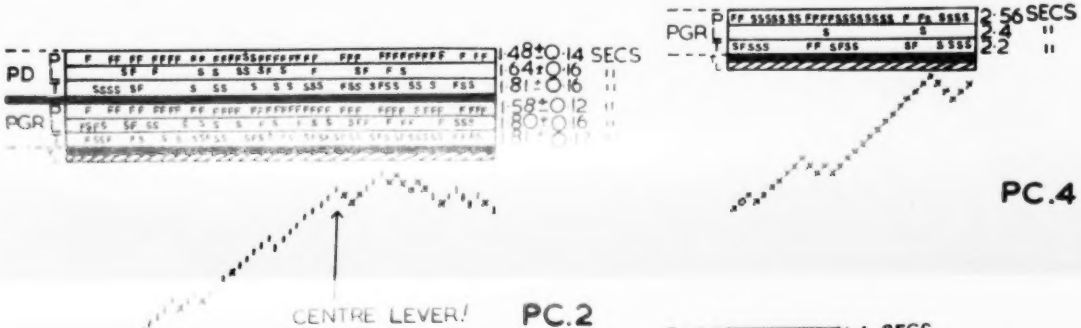
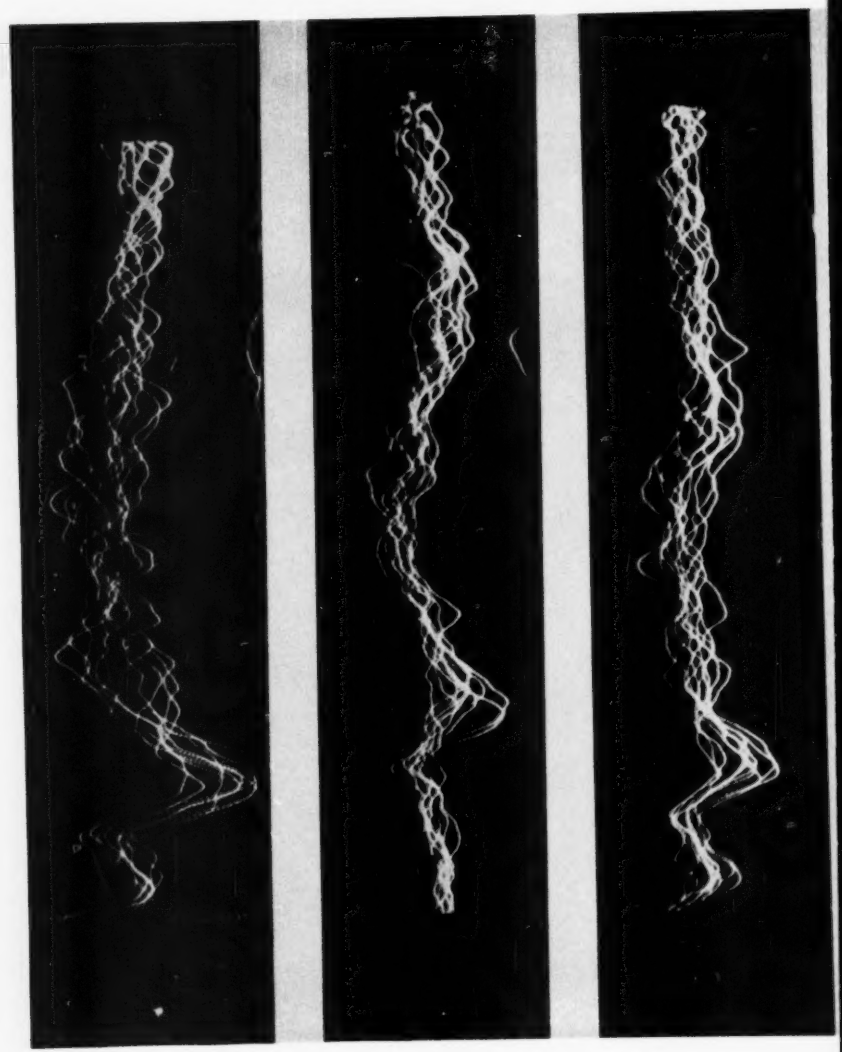


FIG. 2 (A) GSR latencies of patient P.C. In the first series, before treatment, the latencies are all shorter than normal, but the distinction between unconditional and conditional responses is clear. Unconditional responses persist because the subject never attempted to avoid the penalty. After treatment (series 4) the unconditional latencies are markedly increased, the conditional responses are rare and variable. (B) Conditioning curves of patient P.C. The upward trend is misleading – the subject kept the lever on one side and reversed it whenever she heard the penalty (indicated by vertical dashes).





and presentations of tones and flicker alone showed that the subject was now in complete control of the situation and after 139 trials the EEG began to show signs of drowsiness and boredom so the experiment was terminated. In spite of his complete operational success the subject gave a very inaccurate description of the experimental arrangements. His subjective estimate of the time taken for the whole experiment was one-and-three-quarter hours instead of two-and-a-half hours; he was convinced that the aim of the experiment was to muddle him; he described two types of penalty, both very unpleasant, and was sure that the presentation of high and low tones and 'fast' (triple) and 'slow' (double) flashes was in some significant sequence such that he should move the lever to the right after a sequence of three low tones. He admitted he began by random responses, but said he kept trying to catch the sequence of signals, but lost it later. In fact, of course, the order of presentations was random throughout and he only began to succeed when he 'lost' the sequence. This search for significant sequences is quite typical and indeed almost invariable; in these particular circumstances it is, of course, quite futile and indeed eliminates any chance of success. Some subjects who end by responding quite correctly and quickly are still convinced that they are following a sequence which somehow they cannot quite describe.

Returning to the distinction between unconditional and conditional PGR*s* by latency we can see in this typical normal subject that never at any time, even after an unexpected and complete failure, were the PGR*s* as short in latency as the unconditional ones and further, the unconditional responses were just as large and quick at the end of the experiment, when the controls were reversed, as at the beginning. We may infer, therefore, that however this subject, as a representative of a normal population, may have interpreted his experiences, his nervous system was capable at all times of discriminating between events requiring rapid and unconditional response and those of more doubtful and conditional import.

We may now consider the behaviour of two other subjects, in order to see how these observations may illuminate some of the mental aberrations and anomalies related to consciousness.

The first patient, PC, was a woman of 36 with a twelve year history of compulsive thinking associated with fearful delusions with insight. No treatment, either physical or psychological had been effective, and she was referred for implantation of intra-cerebral electrodes and eventual psychosurgery. (FIG. 2).

Before operation her autonomic responses were extremely brisk and over-active; this is reflected in the plot of her PGR latencies. The distinction between unconditional and conditional responses is clear, but all the latencies are very short, about 1.2 and 1.7 seconds instead

of 1.7 and 2.1 in the normal subject. The unconditional responses persist through a hundred trials – there was no attempt at anticipation or avoidance. The learning curve looks quite like that of the first subject: it appears to mount at 45° straightaway, but this is misleading and the curve is made up not of crosses (selective defence movements) but of vertical dashes, indicating that instead of centring the lever after each trial, the patient held it hard over on one side and moved it across to the other whenever the penalty occurred. This tactic ensures that the penalty be received on half the occasions and that the response involve the slowest and largest possible movement. In effect the conditional stimuli were not used at all, although they evoked autonomic and EEG changes. The warnings were assigned no significance and the patient manœuvered herself into an extreme situation from which she could extricate herself only by extreme action at a primitive level.

The procedure was repeated five days after surgical implantation of sixty-eight intracerebral electrodes. Her general condition was unchanged and her behaviour in the conditioning situation was similar. After thirty-six trials she was told positively to centre the lever, after which her response curve became quite horizontal indicating a purely fortuitous series of responses. The only detectable change was in the PGR latency which showed a slight but significant increase to both conditional and unconditional stimuli.

During this period very detailed records were being taken of the intracerebral electrical activity, using a number of techniques to clarify both intrinsic and evoked activity. An account of these observations would form a lecture in itself, but one set of records is of particular relevance; it was discovered by chance that over wide regions in the depths of the frontal lobes in this patient there were non-specific electrical responses to a variety of sensory stimuli. (FIG. 3). These could be evoked by sounds or by visual stimuli and their latency was quite short: 25m.secs for auditory clicks and 35m.secs for visual flashes. The responses to visual stimuli showed a marked tendency to habituation after ten to twenty flashes, but the auditory response persisted unchanged over a series of scores of clicks when there was no concurrent stimulation. When a click was accompanied by a flash, the click response was prepotent, but even the combined response was attenuated during distraction by other stimuli and both click and flash responses were augmented when they acquired extra significance as conditional stimuli. The most striking features of these responses were their very wide dispersion, particularly in the lateral frontal regions of both hemispheres, and their characteristic form – a stereotyped pattern very similar to that found in specific projection regions. Yet these effects were in parts of the

brain as remote as they could be from any specific receiving zone – generally the most taciturn of the so-called silent areas.

Recalling what we have said about the need for a high and controllable selectivity or censorship in the learning brain, we see here evidence for just the opposite, an indiscriminate over-responsiveness, in which everything may mean anything in general and nothing can mean anything in particular. We may presume that the brevity of the autonomic delay and briskness of the responses were also a reflection of the same lack of selectivity and discernment.

As well as being used for recording, the implanted electrodes were used for progressive electrical polarisation within the brain to achieve a limited and reversible leucotomy. After the first trials of this method, which was followed by a rather dramatic loosening up of the patient's tension and delusional fears, the conditioning procedure was repeated for the third time. On this occasion the patient kept the lever central and made one correct anticipation followed by several correct defensive responses, but she broke down in tears after fourteen trials during which there were signs of severe autonomic disturbance. The polarisation treatment was continued in empirically identified brain regions; this was followed by marked general improvement; the delusions disappeared and the patient became quite cheerful and active. The fourth conditioning experiment reflects this change in two ways; the PGR latencies were greatly increased (those to penalty from 1.26 to 2.56 and to tone from 1.7 to 2.2 secs) and the learning curve shows an appreciable gain by defensive conditioning over thirty-two trials. The autonomic changes were minimal, The patient was discharged on probation at this stage, and her subsequent history, though checkered, has confirmed the apparent relation between her mental state, her neurophysiology, and her learning ability.

The second patient PR was studied in similar detail. She is a woman of 60 with a life-long history of migraine overlaid by thirty years of hysterical extension of the syndrome. Her complaint had resisted all therapy, including prolonged psycho-analysis and physical treatment, and her morale had broken during the last three years with depression to a suicidal degree, so that she was referred for intra-cerebral exploration with a view to psychosurgery. Before implantation of the electrodes her behaviour during conditioning was in striking contrast to the other patient P.C. though she also failed completely in associative adaptation. (FIG. 4). The chart of her PGR latencies shows at first a reasonable distinction between unconditional and conditional responses though all the latencies are rather long. The conditional responses to tones faded out after about eighty trials and at this phase the latency of the unconditional responses to the penalty began to

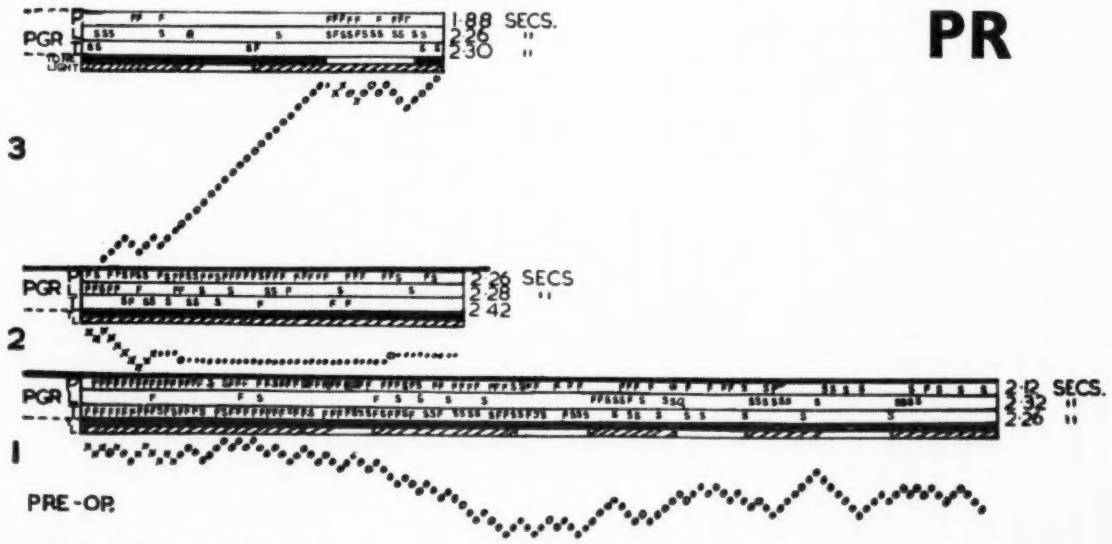
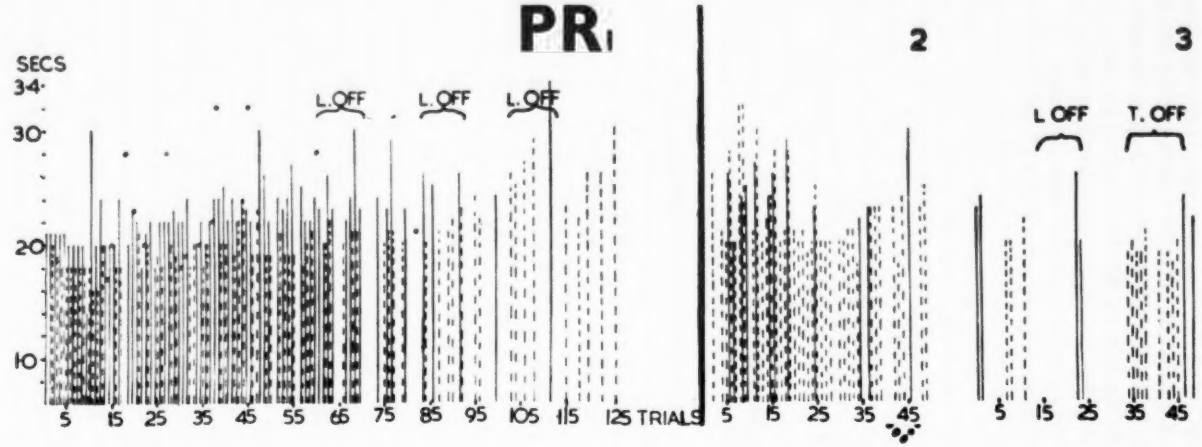

PR
PGR
1·88 SECS.
2·26 "
2·30 "
3
PGR
2·26 SECS
2·28 "
2·42
2
PGR
2·12 SECS.
2·32 "
2·26 "
1
PRE-OP.
TRIALS 8 16 24 32 40 48 56 64 72 80 88 96 104 112 120 128 136

FIG. 4. (A) GSR latencies of patient P.R. In contrast with P.C. all latencies are unusually long and the distinction between unconditional and conditional responses is less clear. At about trial 65 the conditional responses disappear and at the same time the unconditional latencies increase from about 1.8 to 2.8 seconds. (B) Conditioning curves of patient P.R. There was no sign of adaptation over 175 trials. In the first series (before electrode implantation) nearly all responses were anticipatory but quite random and uncorrected by failure. In series 3 after intracerebral polarisation there was a significant sequence of 23 correct anticipations, but this was broken by withdrawal of the tone stimulus. Later series showed no adaptation.



increase and they also diminished in abundance. This effect was so marked that the average latency of the last ten unconditional responses is significantly greater than that of the first ten conditional ones; these changes can be seen particularly clearly when the two types of response are plotted separately. The learning curve is unique in our experience; it shows a completely random response, ending slightly below the starting level. The nature of the response is quite peculiar – from the 13th trial to the 125th all the movements were *anticipatory*, but were entirely at random, and once the lever had been moved to one side it was left there whether or not the penalty occurred. In this way the patient ensured that she received the largest possible chance number of penalties for the longest possible time. A scalp EEG taken just before the conditioning experiment had shown a dramatic frontal spike response to flicker, but this disappeared and during the experiment there were elaborate multiple responses to pattern flicker in the posterior brain regions, but in sharp contrast with the first patient, no indications whatever of diffuse responses.

The experiment was repeated later on the same day with further exhortation and encouragement and on this occasion after eleven trials, twenty-two correct anticipatory avoidance responses were made. At this stage the PGR chart showed reduction in average unconditional latency to 1.88 secs and distinction between this and the conditional latency. Omission of the light CS had no effect, but omission of the tone resulted in random responses. This suggests that in spite of the clear specific responses in the visual pathways, the visual information was assigned no associative significance.

During this period the intra-cerebral electrodes in the orbital regions of the frontal cortex showed persistent delta rhythm attributed to local electrode lesions. The mental condition of the patient improved and remained excellent for some weeks, but she regressed in spite of polarisation of selected frontal sites. The conditioning experiment was repeated on two occasions two months later and showed reversion to the original pattern. In a total of nearly 280 trials all were random anticipations, in spite of emphatic repetition of instructions. At this time the frontal delta rhythms had subsided and the EEG responses to stimulation were stereotyped and restricted to the visual regions.

These three subjects illustrate a number of the points I mentioned earlier. I should perhaps make clear that although the first one is a perfectly normal person and the other two patients with chronic mental disturbance, the three are comparable in *intelligence*, that is in their success in intelligence tests. All three, when told what to do are capable of following instructions quite accurately. The contrast is in their ability to *find things out for themselves*, to come to terms with reality. In the clinical subjects their failure is obvious from the

histories and complaints, but is objectified in their persistent ignorance of the conditioning situation. Even the normal subject, though adaptable, did not understand *how* he had adapted. His consciousness did not include the raw simple facts of the stimuli, but embellished them with a spurious structure of sequences in time. But it is not unusual for people to do the right thing for the wrong reason – superstition and rationalisation are so much a part of all social cultures that they almost seem the mainstay of what we call human nature, as opposed to Nature with a capital N.

Associated with the normal subject's operational success was the clear distinction in his autonomic responses between what we may still call instinctive or unconditional responses and conditional ones. The general staff of his cerebral forces was not involved in tactical decisions, and its strategic management of fresh situations was consequently unhurried, consistent and reserved. Quite on the other hand, the first patient P.C., whose way of living and failure in learning involved a hasty fearful retreat from real and imaginary enemies, showed a comparable impetuosity in defending herself by autonomic reaction; her *conditional* responses were as quick as the unconditional ones in the normal subjects. When there are several possible courses of action and only one correct one, an abnormally rapid decision is likely to be wrong. In the military idiom we would infer that in her case the high command was too pre-occupied with administrative detail to appreciate the strategic situation at all, and was compelled to concentrate all forces at random on one flank and then hastily transfer them to the other. Thus committed, no attack can ever be launched – the central nervous forces are perpetually on the defensive.

This conception is almost too perfectly borne out by the intracerebral recordings; in most frontal regions there were large stereotyped responses to stimuli in all modalities. Those to visual stimuli showed 'habituation' in the sense that the amplitude of the response to monotonously repeated stimuli declined after about half a dozen presentations. But the auditory response persisted unchanged through scores of repetitions in many so-called silent regions. The mechanism of habituation (a misleading term in English where a habit is essentially a *persistent* behaviour trait) is of great interest and importance and may be of more general occurrence than is generally realised[1]. The *absence* of habituation in a non-specific brain region is obviously of serious import, implying, as I suggested above, the incessant pre-occupation of the command centres with trivial and insignificant information. In terms relevant to the theme of this lecture, the consciousness of the patient was out of control, not for lack of contact with the environment, but because of excessive *indiscriminate* engagement with trivial contacts.

In the third subject, whose complaint was of suffering rather than fear, the conditional stimuli gradually lost whatever significance they may have had, and at the same time the central delay in responding to unconditional stimuli increased. In this patient's brain we could find no trace at any time of non-specific responses in frontal areas, suggesting again that the central control was cut off from relevant information by its pre-occupation with suffering. The unconditional penalty began to acquire a significance of its own, as if a commander were less concerned with his strategy or possible victory than with the care of his casualties. The nature of the motor responses in this case was characteristic also; instead of the laconic alternation of the other patient there was a flurried and aimless anticipatory movement, a skirmish with shadows, which was never corrected when proved wrong.

In trying to understand the problems of mentality we must often have recourse to notions which threaten an infinite regression; accepting that within the living brain we must somehow establish working models of the outside world, we are faced with the reflection that this is an image of an image or a model of a model. Are we justified in staring so intently at our own reflection? Surely if it increases our self-knowledge, yes, even if we feel a wave of dizzy bewilderment at the endless vista of diminishing detail. We should remember, too, that our model is not a static one, not a mirror but a mechanism, creating, as it reflects, the wide spectrum of selective patterns that we now call consciousness, and Hamlet the conscience that makes cowards of us all. Here in Shakespeare's birthplace we have seen how in fact the pale cast of thought can corrupt resolution. If I were forced to provide a final aphorism I should say that – apart from the art you practice – consciousness cannot be controlled – it can only control itself.

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Prediction of carbon dioxide tension during anæsthesia

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It is probable that, from the earliest days, concern has been felt about the effect of anæsthetic agents upon the gases carried by the blood. In the eighteenth century, Beddoes[1] noted the change of the colour of the blood: 'I thought it might be an amusing spectacle to see the different tints of blood flowing from a wound by a leech in consequence of breathing different airs. The purple from the nitrous oxide was very evident'. In 1847 Mr Hale Thompson of the Westminster Hospital[2] recorded that '. . . under the full effect of ether, the arterial blood presents its usual appearance. Nor is there any reason from the inhalation to suppose asphyxia can take place, as the usual quantity of air is admitted to the lungs'.

It was appropriate that the earliest thoughts should be directed towards the possibility of oxygen lack rather than to carbon dioxide excess – the former condition being far more dangerous than the latter. However, the use of oxygen enriched gas mixtures has become widespread in anæsthesia and it is now generally realised that, with sufficient oxygen, life may be maintained for limited periods during gross hypoventilation. Interest has, therefore, tended towards the more subtle problem of carbon dioxide homeostasis.

For many anæsthetists, it was the review by Dripps and Severinghaus[3] which first drew attention to the fact that the alveolar carbon dioxide concentration is the result of the balance between production and elimination (rather like the blood urea) and that it may be expressed mathematically by a modification of Bohr's equation:

$$\text{Alveolar } CO_2\% = \frac{CO_2 \text{ output} \times 100}{\text{alveolar ventilation}} + \text{inhaled } CO_2\% \ (i)^*$$

*For the sake of completeness, this equation shows the inhaled carbon dioxide concentration as a parameter influencing carbon dioxide homeostasis. The author believes that, in general, the inhaled carbon dioxide concentration should be effectively zero during anæsthesia and, therefore, this factor is discussed no further. The factors causing rebreathing in anæsthetic circuits are now well understood and there is no difficulty in devising a gas circuit which will eliminate rebreathing.

Radford[4] studied the various factors on the right hand side of equation (*i*) and so derived his nomogram from which it is possible to calculate the tidal volume required to maintain a normal alveolar carbon dioxide concentration (FIG. 1).

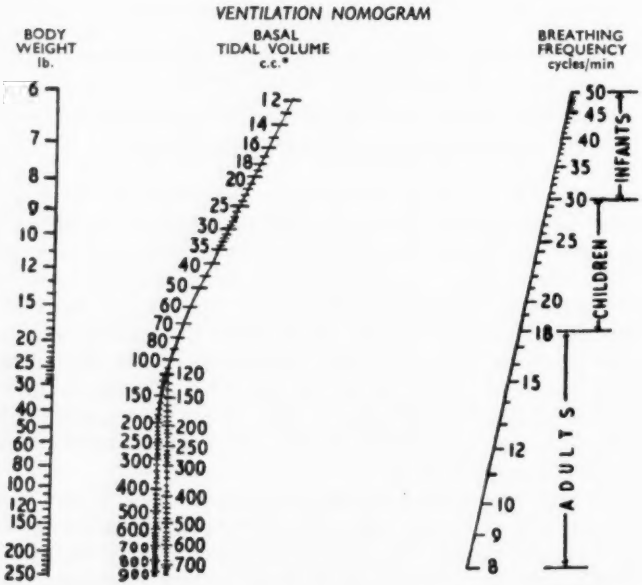

FIG. 1 Radford's Nomogram (Reproduced from *J. appl. Physiol.* (1955). *7*, 451 by permission).

Radford, however, was not concerned primarily with anæsthesia and it is of interest to consider whether his assumptions are valid under the abnormal conditions prevailing during anæsthesia. At the outset, it must be stressed that Radford's nomogram is directed towards carbon dioxide homeostasis of the alveolar gas. This is good enough in the normal conscious subject, breathing spontaneously, but during anæsthesia it is necessary to aim at homeostasis of the arterial blood since it is now well established that, under these conditions, the arterial carbon dioxide tension is higher than the end-tidal or 'alveolar' tension by a mean value of 5mm Hg[5 6 7]. Therefore, the anæsthetist must consider how Radford's nomogram will enable him to predict a ventilation which will ensure homeostasis of the arterial carbon dioxide tension.

VALUES DURING ANÆSTHESIA FOR THE FACTORS ASSUMED IN RADFORD'S NOMOGRAM

The first factor on the right hand side of equation (*i*) is the carbon dioxide output. Radford, not being specifically concerned with anæsthesia, made no allowance for any reduction in carbon dioxide output due to decreased metabolic activity which might occur during anæsthesia. Actually the carbon dioxide output is usually a poor indication of the metabolic activity of the anæsthetised patient as output will equal production only during a steady respiratory state which is quite unusual during anæsthesia. The metabolic activity is, therefore, better shown by the oxygen consumption, which follows the metabolic rate closely.

Table I

Studies of oxygen consumption in the unconscious subject

(expressed as percentage of basal)

1915	Benedict[9]	sleep	87
1951	Shackman *et al*[3]	anæsthesia	85
1958	Campbell *et al*[10]	anæsthesia	88
1959	Furnass[11]	deep sleep	80
1959	Nunn & Matthews[12]	anæsthesia	83

TABLE I summarises the studies of the oxygen consumption made during anæsthesia and sleep. It will be seen that there is considerable evidence for assuming a mean metabolic activity of 85 per cent of basal during anæsthesia. Such evidence as exists[12], suggests that the respiratory exchange ratio (RQ) is normal during anæsthesia and, therefore, in a steady respiratory state, the carbon dioxide output will also average 85 per cent of basal. Radford's nomogram is thus based on a value for carbon dioxide output which is 15 per cent too high during anæsthesia.

However, carbon dioxide output is not the only respiratory parameter which is altered by anæsthesia. In deriving the alveolar ventilation, Radford used values for the anatomical dead space based on the body weight of the patient. Studies during anæsthesia[7] have confirmed that the anatomical dead space in millilitres does in fact approximate to the body weight in pounds. It has also been shown[13] that intubation does effectively halve the personal anatomical dead space as Radford suggested. However, since during anæsthesia the arterial carbon dioxide tension differs from the alveolar tension, it is necessary to derive the alveolar ventilation from the physiological dead space and not from its anatomical component. Two studies[10 7] have now shown that, with tidal volumes close to normal, the physiological dead space is increased by some 70ml during anæsthesia (compared with the conscious state when the anatomical and physio-

logical dead spaces are virtually identical). This implies that reliance upon estimates of the anatomical dead space will result in underventilation by a factor of some 15 per cent at tidal volumes around 450ml. It is, therefore, apparent that, *under the conditions of anæsthesia*, Radford's estimation of carbon dioxide output will tend to cause overventilation by 15 per cent, whilst his estimation of dead space will tend to cause underventilation by 15 per cent. These effects being equal and opposite it would appear that they are likely to cancel one another.

RELIABILITY OF RADFORD'S NOMOGRAM FOR ENSURING ARTERIAL CARBON DIOXIDE HOMEOSTASIS DURING ANÆSTHESIA

As a result of studies of the respiratory dead space during anæsthesia[7] we found ourselves with data which could be used for assessing the reliability of Radford's nomogram in practical use. The data were obtained during routine anæsthesia by measuring the arterial carbon dioxide tension at a time when the ventilation and apparatus dead space were accurately known.

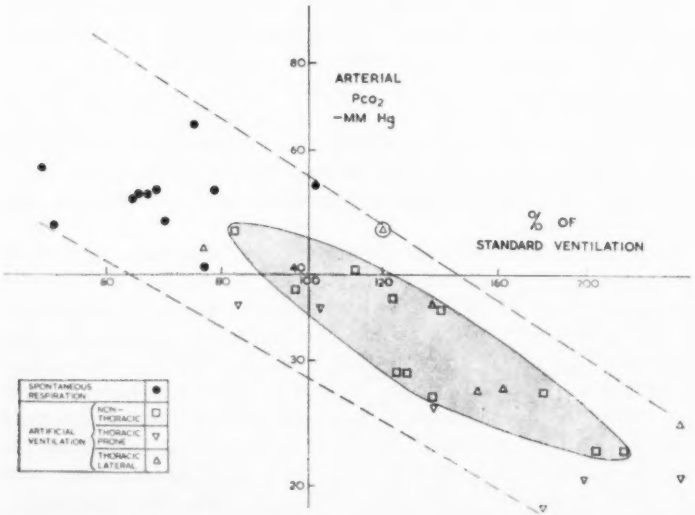

FIG. 2 Arterial carbon dioxide tension plotted against ventilation expressed as a percentage of standard according to Radford[4]. The oval shaded area includes all observations made during artificial ventilation with the chest closed. The ringed symbol represents a patient with emphysema.

FIG. 2 shows the observed arterial carbon dioxide tension plotted against the ventilation expressed as a percentage of the figure derived from Radford's nomogram. Since the expected relationship is reciprocal, the scales are logarithmic so that the relationship between the co-ordinates appears linear rather than as a rectangular hyperbola. It will be seen that the plots of our observations fall within a band which is reasonably straight and whose centre appears to pass through the point of origin of the co-ordinates – that is to say an arterial carbon dioxide tension of 40mm Hg may be expected when the ventilation equals the figure derived from the nomogram. Therefore, it appears that the inaccuracies of Radford's assumptions during anæsthesia do in fact cancel. Although it is apparent that the *mean* error of prediction is small, it is important to note the scatter of individual plots. It is for the individual patient that the accuracy of a prediction is important. The oval area encloses the plots of the patients who were ventilated artificially with the chest closed. The centre of the band passes through the intersection of the co-ordinates, but it is a broad band – the width corresponding to some 15mm Hg. Therefore, it follows that a predicted standard ventilation will result in an arterial carbon dioxide tension which may be 7mm Hg above or below the normal value. This is a figure which is probably acceptable clinically. All the factors which affect the arterial carbon dioxide tension show individual variation and it is only to be expected that any attempt at prediction of the correct ventilation will show some random error.

During spontaneous respiration, the plots are widely scattered, and, in fact, there is no correlation between the arterial carbon dioxide tension and the ventilation. This is probably due to the fact that these patients were in an unsteady respiratory state with carbon dioxide continually passing into or out of the body stores. This is not to say that the nomogram will not give a reasonable guide to the correct ventilation, but it cannot be expected to show the theoretical relationship between carbon dioxide tension and ventilation unless the patient is in a steady state. In our experience this is very difficult to achieve during anæsthesia with spontaneous respiration while a surgical operation is in progress.

Finally, there are the patients undergoing thoracotomy. Here again there is a wide scatter of results which is almost certainly due to the wide variation in physiological dead space which is seen during thoracotomy[7]. This is probably due to position and degree of expansion of the exposed lung which is permitted by the assistant responsible for retraction. Thus we have found small dead spaces when the exposed lung is totally collapsed in the prone position, and large dead spaces in the lateral position when the exposed lung is

relatively free to expand. Since these factors are largely beyond the anæsthetist's control, it would appear that the nomogram is of little value during thoracic surgery.

The findings reported in this paper are in good agreement with the work of Scurr[14]. He compared the concentration of carbon dioxide in gas samples equilibrated with mixed venous blood against the ventilation expressed as a percentage of standard. Allowing for the difference between the carbon dioxide tension of such a sample and that of arterial blood, his results indicated that, taking his patients as a whole, standard ventilation resulted in approximately normal carbon dioxide tensions. Nevertheless, his individual results showed considerable scatter about the mean relationship for the whole group.

AN ALTERNATIVE METHOD OF PREDICTION OF ARTERIAL CARBON DIOXIDE TENSION FROM VENTILATION

By a happy chance, Radford's nomogram shows little systematic error under the conditions of anæsthesia. Since there is little doubt that this is due to the mutual cancellation of at least two invalid assumptions, it appeared reasonable to make use of new values for the determinants of the arterial carbon dioxide which have been evaluated during anæsthesia. These data might then be used as the basis of a method of prediction of carbon dioxide tension specifically for use during anæsthesia.

The method selected is a graphical representation of a variant of equation (*i*). The arterial carbon dioxide tension is plotted against the ventilation for different values of carbon dioxide output which will vary from patient to patient. Armed with such a graph it is possible to

Table 2

Predicted CO_2 output during anæsthesia – ml/min (BTPS)
(Barometric pressure – 760mm Hg)

MALE		15	17	19	20–40	45	55		65		75			AGE
FEMALE			15	16	17	19	20–30	30–40		45	55	65	75	AGE
Body	1.3	178	166	159	155	147	143	142	140	139	135	131	128	
surface	1.4	191	179	171	167	158	154	153	151	150	147	141	138	
area	1.5	205	192	183	179	170	165	164	162	161	156	152	148	
	1.6	218	205	195	190	181	176	174	173	171	166	162	158	
Sq m.	1.7	232	218	207	203	192	187	185	184	182	177	172	167	
	1.8	246	230	220	214	203	198	196	194	193	187	182	177	
	1.9	260	243	232	226	215	209	207	205	203	198	192	187	
	2.0	275	256	244	238	226	220	218	216	214	208	202	197	
	2.1	287	269	256	250	237	231	229	227	225	218	212	207	
	2.2	301	282	268	262	249	242	240	238	235	229	222	217	
	2.3	315	294	281	274	260	253	251	248	246	239	232	227	

read off the expected carbon dioxide tension for any ventilation or, alternatively, to select the ventilation required to produce any carbon dioxide tension which the anæsthetist feels would be suitable. Not all anæsthetists are agreed that the normal carbon dioxide tension is the best during certain operations.

The first step is to arrive at an estimate of the probable carbon dioxide output of the patient. TABLE 2 shows the expected carbon dioxide output of an anæsthetised patient based on age, sex and body surface area.* Without doubt, body weight could be used instead of surface area[4]. These values are actually the metabolic production of carbon dioxide and the output will equal the production only in a steady state. The values given are 86 per cent of basal carbon dioxide production according to established values for basal metabolic rate and assuming an RQ of 0.82[15 16].

The relationship between arterial carbon dioxide tension and alveolar ventilation may be represented by a family of rectangular hyperbolas, each representing a different value for the carbon dioxide output (FIG. 3). The carbon dioxide output for a particular patient

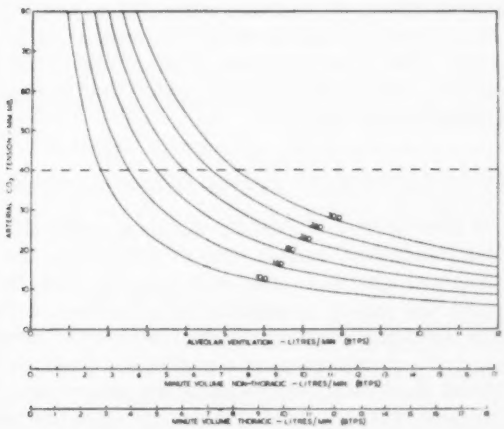

FIG. 3 Relationship between arterial carbon dioxide tension and alveolar ventilation for different values of carbon dioxide output. Additional scales along the abscissa show minute volume as explained in the text.

having been predicted from TABLE 2, the relationship between carbon dioxide tension and ventilation for that patient may then be seen at a glance. It is at once apparent that a small reduction of a low ventilation

will result in a large increase in carbon dioxide tension while an increase in a high ventilation will have relatively little effect upon the carbon dioxide tension.

The practical value of alveolar ventilation as the abscissa is limited since alveolar ventilation cannot be measured directly. It is, therefore, important to relate the alveolar ventilation to the minute volume which can be measured without undue difficulty. Since we are concerned with the arterial carbon dioxide tension, the alveolar ventilation must be calculated from the minute volume using the physiological dead space as defined by Enghoff[17] – that is by solution of Bohr's equation, but substituting the arterial carbon dioxide tension for the alveolar carbon dioxide concentration. In many ways the use of the physiological dead space is simpler than Radford's use of the anatomical dead space since it appears that the physiological dead space is a fairly constant fraction of the tidal volume during anæsthesia[7]. From this it follows that the alveolar ventilation is a constant fraction of the minute volume, the factor being approximately 0.7 in the case of extra-thoracic surgery and 0.6 during thoracic surgery. It is now possible to insert minute volume under these two conditions as additional co-ordinates along the abscissa of FIG. 3. Having predicted the carbon dioxide output of a patient from TABLE 2, FIG. 3 may be used to relate the arterial carbon dioxide tension directly to the minute volume. It should be stressed that the relationship is only valid in the intubated patient and in the absence of rebreathing of carbon dioxide.

RESULTS OF PREDICTION USING ALTERNATIVE METHOD

The value of this method of prediction was assessed by using the values for arterial carbon dioxide tension obtained in the group of patients mentioned above. In this case the observed tension was compared with the tension predicted from the minute volume. In FIG. 4 the predicted and observed tensions are plotted along the two axes so that if the correlations were perfect the plots would all lie along the line of slope one. Unfortunately this was not so. The mean error of prediction was very small, but for the individual patients the scatter was considerable, the 95 per cent confidence limits being of

*In TABLE 2, values for carbon dioxide output are given at body temperature and pressure, saturated with water vapour, assuming the body temperature to be 38°C and the barometric pressure 760mm Hg. Should the barometric pressure differ from 760mm Hg any error introduced will disappear when the table is used in conjunction with FIG. 3 in which the same assumptions are made. There is, therefore, no need to know the barometric pressure when FIG. 3 and TABLE 2 are used together.

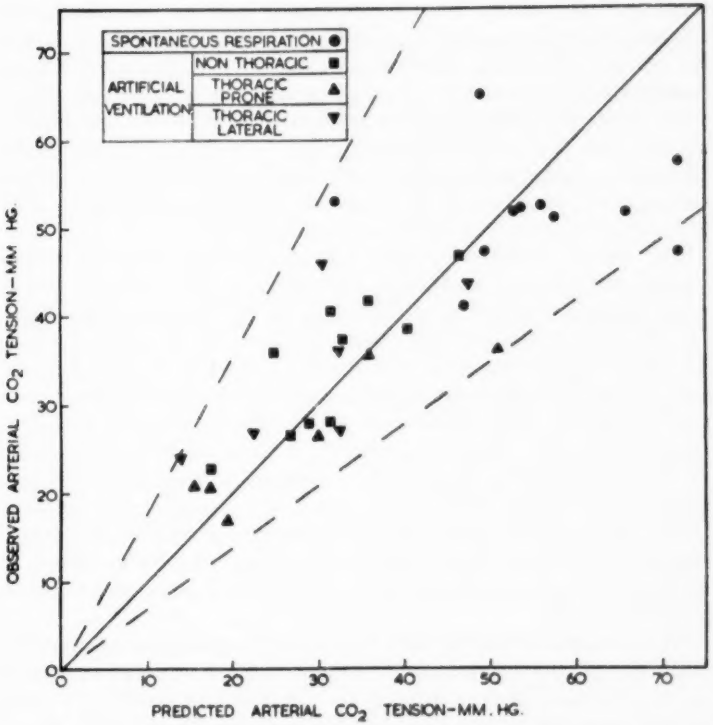

FIG. 4 A comparison of predicted with observed arterial carbon dioxide tension. The line has a slope of one and the dotted lines indicate two standard deviations of the error in prediction.

the order of $\pm$ 40 per cent of the predicted tension. Clearly a prediction with this possible random error is almost worthless and little better than an inspired guess. However, as with Radford's nomogram there was noticeably less scatter in the group of patients who were ventilated artificially with their chests closed.

SOURCES OF THE SCATTER IN VENTILATION NOMOGRAMS

It would appear that the value of ventilation nomograms during anæsthesia is severely limited by the wide variation in the accuracy of the predictions from one individual to another. It is, therefore, of interest to examine the sources of this scatter.

The carbon dioxide output may differ from the mean value both as a result of variation from the mean metabolic activity, and as a

result of discrepancy between production and output due to an unsteady respiratory state. In general the unsteady respiratory state is the greatest obstacle to prediction of carbon dioxide output during anæsthesia – particularly during spontaneous respiration. Even after twenty minutes of uniform artificial ventilation carbon dioxide outputs have been recorded varying from 73 to 109 per cent of basal. During the prolonged ventilation of patients with respiratory failure the output should come to equal the production and it is possible that the metabolic activity would show less variation.

The second source of scatter is in the relation between minute volume and alveolar ventilation. This depends upon the ratio of the phsyiological dead space to tidal volume. In common with other biological quantities this ratio shows a scatter about its mean value. The mean value of the ratio in twenty-three extrathoracic studies was found to be 0.32 with a standard deviation of 0.07[7]. Thus the 95 per cent confidence limits of alveolar ventilation are from 0.54 to 0.82 times the minute volume. The coefficient of variation is of the order of that of the carbon dioxide output and will, therefore, contribute equally to the scatter. However, during thoracic surgery, the variation in the physiological dead space is much greater still (SD=0.11) for reasons which have been mentioned above. This factor alone is sufficient to limit severely the value of ventilation nomograms during thoracic surgery.

In summary, it may be said that during spontaneous respiration, prediction of the arterial carbon dioxide tension of an anæsthetised patient is rendered very difficult by the unsteady respiratory state which is usually present. Radford's nomogram should still give a reliable guide of what is an adequate ventilation, but it should not be expected that a correlation will always be shown between the arterial carbon dioxide tension and the ventilation expressed as a percentage of standard.

During artificial ventilation with the chest closed, prediction of carbon dioxide tension is reasonably satisfactory and there is fairly good correlation between the tension and the ventilation. Radford's nomogram should give a reliable indication of the correct ventilation.

During thoracotomy there is poor correlation between carbon dioxide tension and ventilation, largely due to variation in the physiological dead space. Ventilation nomograms will be almost valueless in these circumstances and the arterial carbon dioxide can be ascertained only by direct measurement.

Acknowledgements

I am indebted to the surgical and anæsthetic staffs of the Whittington Hospital and Harefield Hospital. The observations were made on patients under their care.

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The experimental and clinical use of profound hypothermia

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In clinical hypothermia it has hitherto been usual to cease cooling at 28 – 32°C. At this temperature eight to ten minutes circulatory arrest is permissible, but longer periods involve an increasing risk of permanent cerebral damage.

Attempts to lower body temperature further and thus extend the period of circulatory arrest available have usually been defeated by circulatory failure or ventricular fibrillation.

Anti-fibrillatory agents such as quinidine, procaine or carbon dioxide have been used to prevent ventricular fibrillation. An alternative method has been the use of a pump oxygenator to maintain the circulation while cooling is continued.

Niazi and Lewis[1] described clinically induced hypothermia achieved by surface cooling to 9°C with circulatory arrest of forty-five minutes. The patient suffered from advanced carcinomatosis and it was hoped that profound hypothermia might retard the rate of tumour growth. The patient recovered fully from this procedure, but her malignant condition was unaffected. Gollan[2] has used a pump oxygenator and extracorporeal heat exchanger to cool animals to 0°C and Kenyon and Ludbrook[3] and co-workers have recently described their results in dogs using a similar method.

There have also been reports from several centres of the clinical use of pump oxygenators combined with hypothermia. This technique has been used in order to permit the use of low flows during cardiopulmonary bypass, rather than arrest of the circulation.

Using the method devised at Westminster Hospital[4 5] we have successfully cooled children and adults to the region of 14°C, measured in the pharynx and we have achieved periods of complete circulatory arrest of up to fifty-two minutes. The method utilizes an

Substance of a paper read at the Annual Meeting of The Association of Anæsthetists at Stratford upon Avon on 23rd October 1959

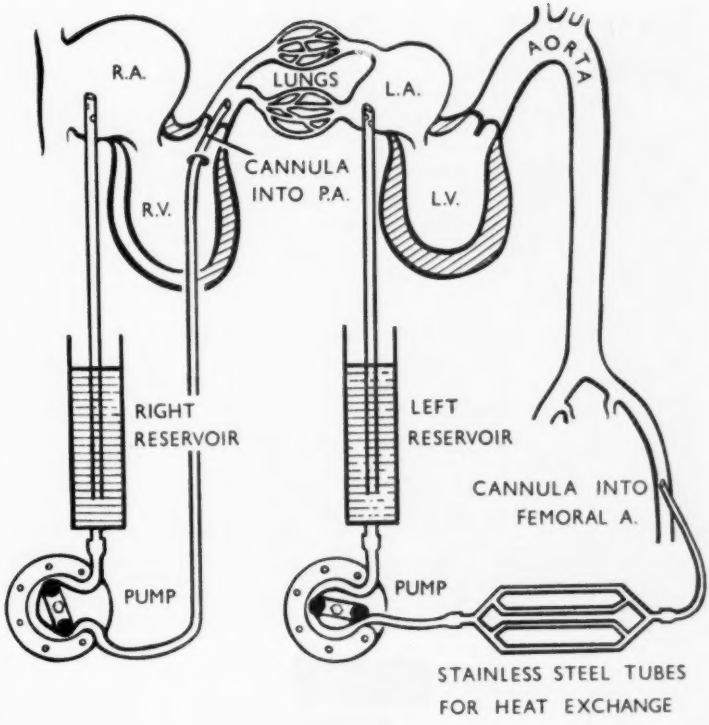

FIG. 1

extracorporeal circuit and a heat exchanger, but continues to use the lungs as an oxygenator (FIG. 1).

A cannula is inserted into each atrium. From the left atrium blood is drained into a reservoir whence it is pumped via a heat exchanger, into the femoral artery. Water at 3° – 4°C cools the blood in the heat exchanger and this cold blood entering the circulation, cools the body. Those organs with a high blood flow, such as the brain and heart, are cooled most rapidly.

At a temperature of about 29°C pharyngeal, cardiac action becomes inadequate either as a result of bradycardia or of ventricular fibrillation.

Drainage of blood from the right atrium into the second reservoir is then commenced and this blood is pumped through a cannula into the pulmonary artery and thus onwards through the lungs. This cannula is inserted via a stab incision in the outflow tract of the right ventricle.

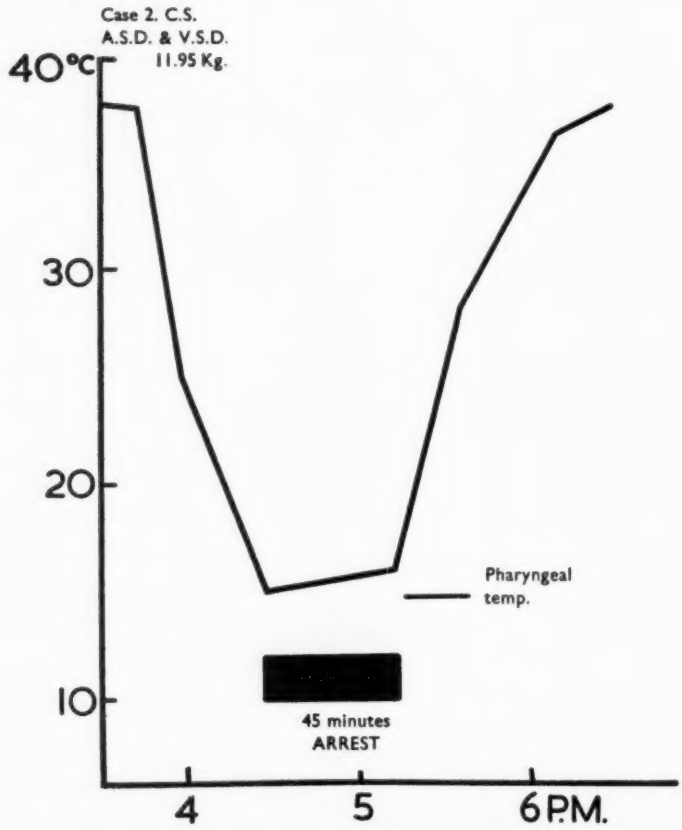

FIG. 2. Record of temperature changes during operation

At approximately 14°C pharyngeal temperature, the pumps are stopped and the venous drainage lines clamped. Thus complete circulatory arrest ensues and artificial ventilation may be discontinued.

The heart is opened and surgical correction of the defect completed. Air is excluded from the heart, any cannulæ that may have been moved are replaced in position and the heart is closed.

The pumps and ventilation are restarted and atrial drainage recommenced. Water at 40°C is circulated through the heat exchanger.

The body temperature rises rapidly and when cardiac action is satisfactory, the pumps are stopped and the cannulæ withdrawn.

I would now like to consider in more detail some special aspects of this technique and some of the problems raised.

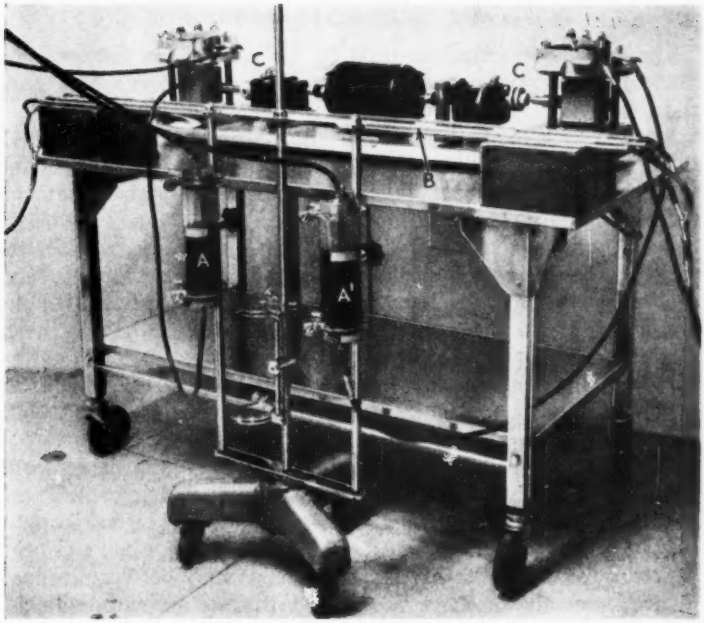

FIG. 3A A and A^1 – Right and left venous reservoirs
B – Stainless steel heat exchanger tubes
C – Roller pumps

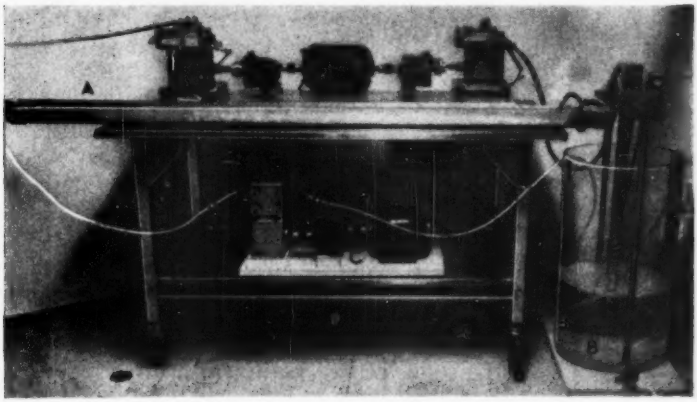

FIG. 3B A – Trough containing heat exchanger tubes
B – Reservoir for water at 40°C
C – Pump for water in trough

ANÆSTHETIC TECHNIQUE

The anæsthetic technique used by Dr Scurr is as follows: premedication is with pethidine 10mgm/stone, phenergan 5mg/stone and atropine.

Anæsthesia is induced with intravenous thiopentone and succinylcholine is used for intubation. In children, nitrous oxide-oxygen and cyclopropane for induction, followed by intravenous or intramuscular succinylcholine is sometimes more suitable.

Anæsthesia is continued with light ether and oxygen while the patient is being weighed, positioned on the table, and the recording devices put in place. The intravenous drip is also set up, the femoral arteries exposed at the groin and one artery is catheterized to provide a central aortic pressure recording.

During the thoracotomy, anæsthesia is continued with nitrous oxide and oxygen and muscle movement is prevented with d-tubocurare.

Nitrous oxide may be discontinued when the pharyngeal temperature begins to fall. Ventilation is continued during cooling and rewarming with 5 per cent carbon dioxide and 95 per cent oxygen. Carbon dioxide is discontinued during rewarming when the heart action is well established and nitrous oxide may be recommenced.

More recently we have abandoned the use of carbon-dioxide without apparent ill-effect.

Vigorous spontaneous respiratory movements often begin at 18 – 20°C. These may decrease or disappear as the body temperature rises further and it is possible that this may be an example of recurarisation on rewarming similar to that observed by Zaimis[6].

Atropine and prostigmine have been given at the end of the operation when indicated, often with improvement in respiratory movements.

Ventilation during circulatory arrest is discontinued as it serves no useful purpose and may squeeze blood out into the operative field and lead to air trapping in the pulmonary veins.

No difficulty has been experienced in re-expanding the lungs and bronchial suction has shown the lungs to be remarkably free of secretions.

This is in marked contrast with our experience with the Lillehei-de Wall bubble oxygenator when blood stained secretions were often obtained from the lungs at the end of the operation.

Control of coagulation

Heparin 1.5mgm/kg is given prior to cannulation and its action is reversed with Protamine 3mgm/kg after the cannulæ have been removed.

Three to four pints of heparinised blood is used in priming the machine.

No obvious bleeding tendency has been observed in these patients post-operatively.

Blood balance

It is important to replace blood losses adequately. If this is not done, hypotension and diminished venous return may result during perfusion.

Blood losses are made up as they occur with intravenous citrated blood. During perfusion further losses may be replaced intra-arterially from the reservoirs; it may be necessary to add further heparinised or citrated blood to the reservoirs for this purpose.

Careful blood balance records are kept at all stages of the operation and compared finally with the patient's change of weight and the clinical state.

Allowance should be made for the fact that approximately 20 per cent of each bottle of citrated blood replaced consists of watery citrate solution; extra blood should therefore be given.

The heart

At cardiac temperatures below 30°c cardiac rhythm tends to be

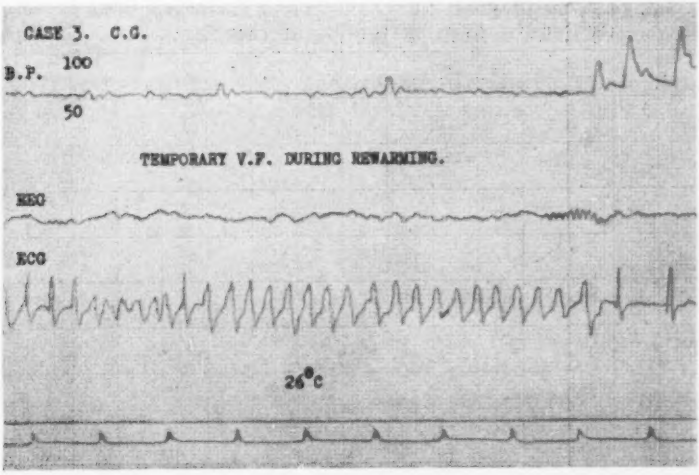

FIG. 4 This trace shows unstable cardiac rhythm during rewarming with periods of ventricular ectopic rhythm giving way to ventricular fibrillation, ventricular tachycardia and finally sinus rhythm. The upper trace shows the appearance of systolic peaks on the aortic pressure trace as soon as effective cardiac action begins. The EEG trace shows early return of activity.

unstable and ventricular fibrillation may become established. It may revert spontaneously to co-ordinated ventricular rhythm during cooling, arrest periods or rewarming, but permanent reversion is most likely to occur late in rewarming. (FIG. 4.)

If electrical defibrillation is necessary it is most likely to produce stable rhythm if carried out at temperatures between 30 – 34°C during rewarming.

Often ventricular fibrillation is not seen at any time during the operation, particularly in young children. Thus of fifteen children under 7 years old, four did not fibrillate, eight others fibrillated, but reverted spontaneously to normal rhythm during rewarming and only three hearts needed electrical defibrillation. One heart reverted to normal rhythm when the ventricular surface was lightly flicked with a finger.

In older children and adults, ventricular fibrillation is more frequent and electrical defibrillation more often necessary.

Very prolonged ventricular fibrillation is no bar to successful defibrillation, provided the heart is warm, well oxygenated and not over distended. In some cases the ventricles have fibrillated during the period of cooling, arrest and rewarming for as long as two and a half hours, but restoration to normal rhythm has been achieved without difficulty.

The electrocardiogram during ventricular fibrillation often shows a characteristic wave form of groups of complexes (FIG. 5). This

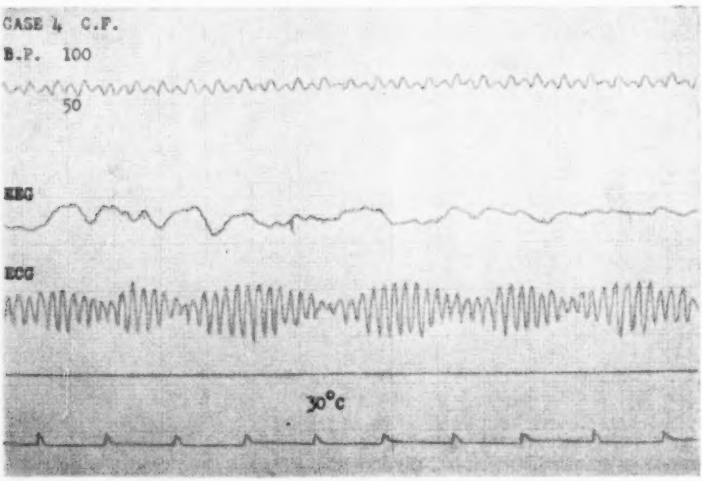

FIG. 5 Electrocardiograph during prolonged ventricular fibrillation.

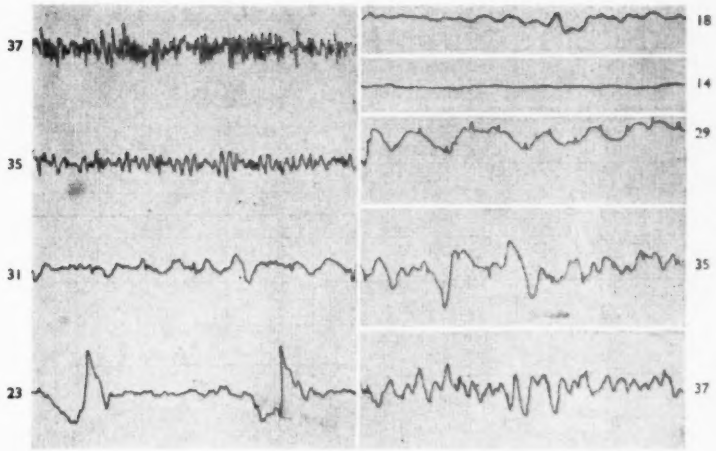

FIG. 6 Electroencephalograph changes at different temperatures (°C).

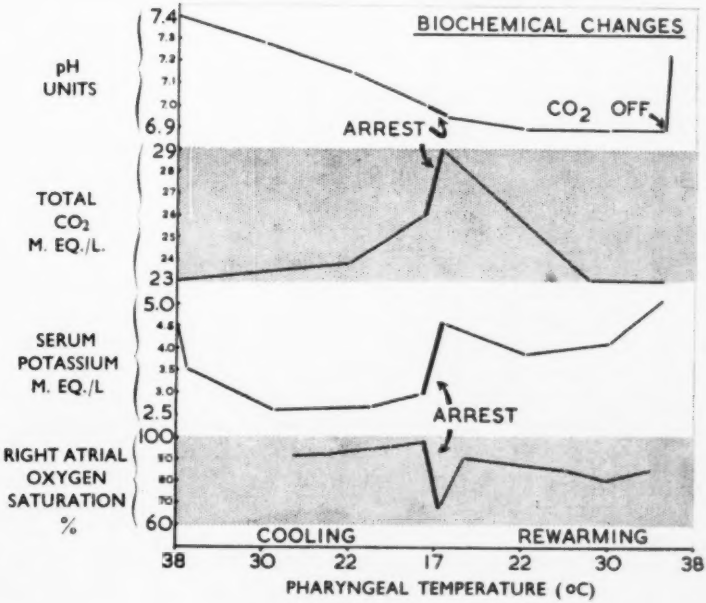

FIG. 7

electrocardiogram seems to carry a good prognosis and we have often noted spontaneous defibrillation occurring in these hearts when this pattern has become well established.

The *electroencephalogram* usually disappears at 18 – 20°C. and reappears at about 22°C. pharyngeal. A typical series of traces at various temperatures is shown in FIG. 6. The electroencephalogram is simple to apply and experience has shown that it provides a useful early warning of disturbances of cerebral oxygenation.

The *biochemical changes* have been investigated in these cases, and FIG. 7 shows changes in pH, total carbon dioxide and serum potassium in a single case. The temperature of the samples was restored to 38°C. for pH determination. They show temporary alterations, but pre- and post-operative values are nearly always closely similar.

pH changes have been much smaller in our more recent cases when carbon dioxide has not been administered.

The physiological importance of these changes is difficult to evaluate at this stage.

Oxygen saturation of blood returning to the right atrium from the tissues shows a rise to 97 per cent at 14°C. followed by a fall to 68 per cent at the end of arrest period and then a rapid rise during early rewarming with a further slight fall as metabolism increases later in rewarming.

Perfusion

At the commencement of perfusion, only the left sided circulation is in use. The pump output is set to give a flow of 150 – 1000cc/min depending on the patient's weight and a clip on the venous line is adjusted so that blood flow from the left atrium into the reservoir balances the pump output from the reservoir into the femoral artery. This allows fairly slow and even cooling of the body and avoids upsetting the cardiac rhythm too early on. Should circulatory insufficiency, due to ventricular fibrillation, bradycardia or hypotension, occur at any stage it is a simple matter to insert the pulmonary artery cannula and begin the right sided circulation. As the clips on the atrial lines are gradually released, the pump flows are increased, until flow into the femoral artery reaches 60 – 100cc/kg/min. This flow assures oxygenation and further rapid cooling. Mean blood pressure is usually between 60 – 120mm Hg.

Flow rates on left and right pumps are kept approximately equal, but variations are not important as long as left flow is adequate and as long as the reservoir levels remain constant.

If there is functional pulmonary and tricuspid valve incompetence, this may result in recirculation taking place in the right circuit and a flow rate greater on the right side than the left.

Recirculation, with a flow greater on the left side than on the right, may occur when there is a shunt between aorta and pulmonary artery. This has been noticed in Fallots Tetralogy, presumably due to the bronchial anastomosis and may also be expected in the presence of a patent ductus arteriosus.

We do not take venous pressure recordings because the state of the right and left atria may be observed directly during perfusion.

Over distension of the right atrium may be due to mechanical obstruction to the right atrial cannula, to over transfusion or to excessive left pump flow which will result in excessive venous return to the right atrium.

A very flat right atrium may be due to the reverse situation of under transfusion or too low flow rate from the left pump. All these faults may be rapidly corrected.

During rewarming, the left flow is kept at 60 – 100cc/kg/min and usually right and left flows are similar. With these high flow rates rewarming proceeds rapidly to 34°C. pharyngeal and oxygenation is assured.

Electrical defibrillation is carried out at about 32°C. if it is necessary and when the heart is beating well, the right circulation is discontinued and the right atrial and pulmonary artery cannulæ withdrawn.

The left flow is then slowly reduced and the left atrial drainage is progressively clipped off as this is done. Thus the left ventricle receives gradually larger quantities of the left atrial blood and its stroke output improves. In due course pulse beats begin to appear on the arterial trace above the line pressure of the pumps.

If the heart seems able to maintain an adequate pressure the left circulation may be gradually discontinued and all cannulæ removed.

RESULTS

The results achieved using this method at Westminster Hospital are shown in the table (FIG. 8).

CARDIAC DEFECT	NO. OF CASES	DIED
Atrial septal defect	1	0
A S D with pulmonary valve stenosis	1	0
A S D with ventricular septal defect	1	0
Ventricular septal defect	9	2
Subaortic stenosis	1	0
Mitral stenosis	1	0
Mitral incompetence	1	1
Fallot's Tetralogy	3	2
Undiagnosed abnormality	1	0
Atrio-ventricular canal		
complete	1	1
incomplete	2	0
TOTAL	22	6

FIG. 8.

All these cases were considered unsuitable for operation under moderate hypothermia.

The general condition of the patients post-operatively has been encouraging. None have shown any evidence of metabolic or cerebral disturbances despite periods of circulatory arrest of up to fifty-two minutes.

Psychiatric assessment has shown no evidence of personality changes or other mental disturbances.

Two children with ventricular septal defects died following heart block. Both had very large defects, and one child weighed only eight pounds.

One case of Fallots Tetralogy had a satisfactory course for nine days post-operatively except for attacks of paroxysmal tachycardia and then died suddenly. At post-mortem the ivalon patch covering the ventricular septal defect had become partially detached. The other Fallot also recovered full consciousness, but was noted at operation to have a very thin left ventricle. She developed persistent heart block and hypotension and died twenty-four hours later.

The complete A-V canal was a very extensive lesion with a large ASD, VSD and split mitral and tricuspid valves. Repair was only partial and the child died a few hours after the operation.

The other death in the series occurred during rewarming due to the pulmonary artery cannula producing a dissecting hæmatoma of the pulmonary artery. This was caused by an error in surgical technique.

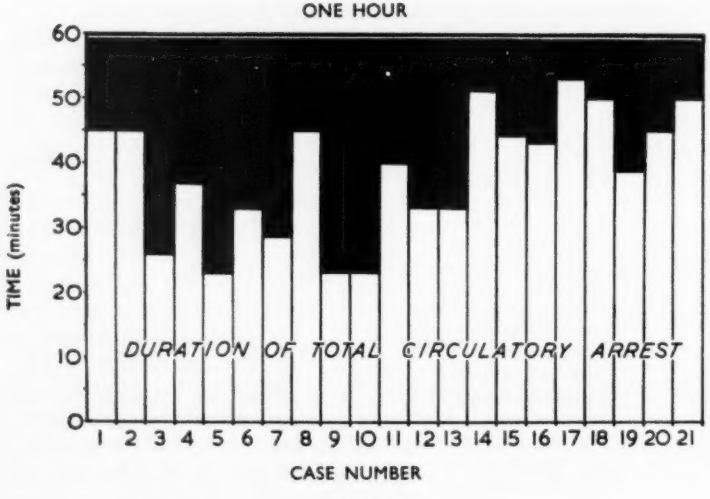

FIG. 9

The periods of arrest achieved in our cases are shown in FIG. 9. We do not yet know the maximum period of arrest available to us at 14°C. but it is certainly at least fifty-two minutes.

It is our opinion that the fatalities have not been due to the hypothermic technique; they have been due to attempts to operate on severe and virtually inoperable cardiac disease coupled with lack of experience in dealing with certain surgical problems concerning the repair of defects and cannulation.

SUMMARY

We feel that profound hypothermia with prolonged arrest of the circulation is a safe procedure and that the method described may be safely applied in cardiovascular surgery.

Acknowledgements

The experimental work on this method was carried out in the Department of Experimental Surgery under the direction of Mr C. E. Drew in association with Mr G. Keen. I am grateful to Mr Drew and Dr Scurr for their advice and comments on this paper. Biochemical determinations were carried out by Dr P. Cliffe, Dr J. Hoyle and Dr D. James.

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Drugs which stimulate affective behaviour

2 Comparison of the analeptic effect of d'amphetamine, bemigride with amiphenazole, methylphenidylacetate, iproniazid (micoren) and RP8228

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The analeptic effect of d'amphetamine is well known. Its use in clinical anæsthesia and for barbiturate intoxication is limited because the effective dose range often produces toxic cardiac reactions (heart block) with severe hypertension or hypotension, and tachyphylaxis develops quickly[1]. Three other drugs have been used in the past few years to produce a reduction in recovery time from barbiturate narcosis or intoxication. These are reported to cause marked stimulation of respiration without greatly affecting the circulation, or causing vomiting or convulsions or other severe manifestations of cerebral stimulation.

Bemigride (megimide; β ethyl–β–methyl–glutarimide) and amiphenzole (daptazole; 2:4 diamino–5–phenylthiazole hydrochloride) are made by the A. Nicholas Products Laboratories Ltd. They are colourless crystalline compounds which are poorly soluble in water. Bemigride has been shown to reduce the sleeping time from the intravenous injection of 20mg/kg of thiopentone in dogs by approximately 25% when 10mg/kg is injected immediately after the thiopentone[2]. An overdose of bemigride causes fasciculation and convulsions, but the dose required for such a toxic reaction is far in excess of the effective dose[3]. Amiphenazole is only a weak antagonist of barbiturates. However, it has been recommended in the treatment of barbiturate poisoning in combination with bemigride, as the combined effect appears to be more active than bemigride alone[4]. The difficulty of proving the analeptic effectiveness of these two drugs in clinical practice is shown by the different results that have been reported[5-10]. Most of the data indicate that both of these drugs have an effective analeptic action against barbiturate narcosis in subconvulsive doses.

These two preparations have not been used in clinical medicine to treat other depressed states.

Methylphenidylacetate (ritalin; methyl-(α phenyl-2-piperidyl)-acetate hydrochloride) is a white crystalline compound which is soluble in water and has a pH of 3 in 10 per cent aqueous solution. A dose of 1mg/kg causes an increase in spontaneous activity in dogs with maximum restlessness in about one hour, then gradual recovery without serious untoward effects. Methylphenidylacetate (10 to 30mg/kg) has been used with variable success to elevate the mood of patients who are metally depressed. However, it appears to be quite effective in reversing light barbiturate narcosis[11-15].

Three more substances are available that may have efficacy for the reversal of barbiturate narcosis: iproniazid, prethcamid and RP8228. The main objective effect of these drugs is stimulation of respiration. They are not related chemically and are also different in action from d'amphetamine in that they do not cause potent central nervous system stimulation. They also lack the convulsive activity of picrotoxin and pentamethylenetetrazol, and the intense but brief effect on respiration and vasomotor reactivity that is seen with nikethamide and α lobeline.

Iproniazid (marsilid; 1-isonicotinyl-2-isopropylhydrazine) was synthesised in the Roche Laboratories by Fox in 1951[16]. It is a white crystalline substance which is stable in dry form and is highly soluble in water. Doses of 40mg/kg intravenously to unanæsthetised dogs produce no observed effects. Doses of 50 to 100mg/kg causes hyperactivity and increases electroencephalographic amplitude in thiopentone-decamethonium anæsthetised dogs[17].

This drug was originally introduced for the treatment of tuberculosis. During such therapy in man it was observed that iproniazid caused mild stimulation of the central nervous system as evidenced by an improvement of the patient's mood, an increased response to external stimulation and increased muscle tone. The specific mode of action of iproniazid is thought to be partly through inhibition of monamine oxidase and increase of serotonin in the brain[18].

Of particular interest to the anæsthetist was the observation that in addition to psychic stimulation, iproniazid appeared to potentiate the effect of other drugs, such as the sympathomimetic amines and barbiturates[19 20].

Prethcamid (micoren) is a mixture of equal parts of two aliphatic amines: n-crotonyl-α-ethylaminobutyric acid dimethylamide and n-crotonyl-α-propylaminobutyric acid dimethylamide in an aqueous solution in which one ml of the preparation contains 75mg of each substance. This solution is supplied by the pharmaceutical department of the J. R. Geigy firm in Switzerland.

The analeptic effect of this preparation has been compared to that of nikethamide and pentamethylenetetrazol by Nuki and associates in Japan who found that prethcamid had a much higher therapeutic index. They showed that in animals prethcamid exerts an effect on the central nervous system which is capable of abolishing anæsthesia without causing convulsions. It increased the depth of respiration without significant change in the blood pressure in normal dogs (0.05ml/kg). In rabbits who were bled or deeply anæsthetised there was a prompt improvement in the blood pressure and respiration after prethcamid. Several clinical reports showed that prethcamid was a reliable and powerful stimulant in respiratory depression of central and reflex origin and it caused persistant reversal of respiratory depression due to morphine, pethidine, thiopentone and hexobarbitone. This was in marked contrast to the transitory effect of α lobeline[21-27].

RP8228 was prepared in the research laboratories of Rhône Poulenc-Specia in France. It is the hydrochloride of the lævo isomer of 1–phenyl–1–(2′–piperidyl)–1–acetoxy methane and occurs as a white finely crystalline powder which is soluble in water and methanol. This compound was suggested for therapeutic trial because it was shown to be capable of improving the function of the centres of perception and association; of facilitating mental and physical work; and of counteracting depression and somnolence. It was free of sympatheticotonic and thyrotropic effects and did not impair functions of vital organs, nor did it cause visceral damage.

Daily administration of 5mg/kg by mouth to dogs caused psychomotor excitation only after 15 days of treatment. Intoxication at sub-lethal doses was marked by co-ordinated hyperactivity without a subsequent stage of depression. Toxic doses produce tremor and inco-ordinate convulsion. RP8228 has little or no effect on blood pressure, cardiac rhythm, or on respiratory rate and amplitude, but produces stimulation of locomotion in dogs, without subsequent depression, at a dose level of 5mg/kg. Its application in anæsthesia stems from its apparent antagonism to barbiturate narcosis. Intravenous injection of RP8228 rapidly wakens rats under light pentobarbital narcosis. It was ineffective during deep anæsthesia with barbiturates or diethyl ether[28].

METHOD

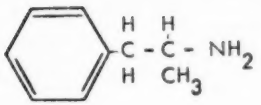
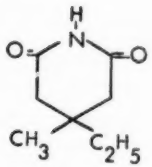
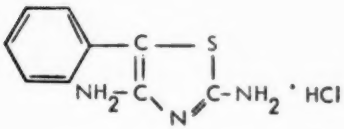
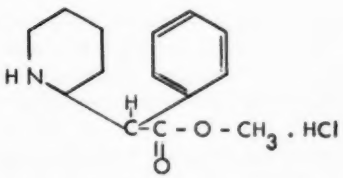
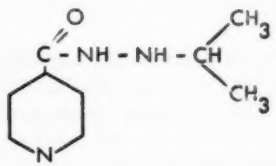
This report deals with a comparison of these agents as analeptics against thiopentone narcosis. TABLE I shows the structural formula and dose level of each drug that was tested.

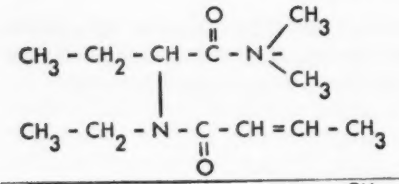
The dose level selected for each drug was that which usually produced an optimum analeptic response when injected in a single

intravenous dose, without causing twitching or other undesirable reactions. In every experiment the dog received 25mg/kg of thiopentone intravenously in a 2 per cent solution injected rapidly.

Table I

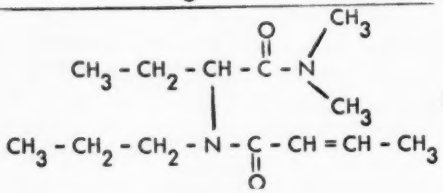
Analeptic Drugs

STRUCTURAL FORMULA	OFFICIAL NAME TRADE NAME CHEMICAL NAME	DOSE TESTED MG/KG
	d'amphetamine dexedrine β–phenyliso-propylamine	0.1
	bemigride megimide β–ethyl–β–methyl-glutarimide	5
	amiphenazole daptazole 2:4 diamino-phenylthia-zole . HCl	5
	methylphenidyl-acetate ritalin methyl–(α phenyl–2–piperidyl)–acetate . HCl	1.0
	iproniazid marsilid 1–isonicotinyl–2–isopropyl-hydrazine	25

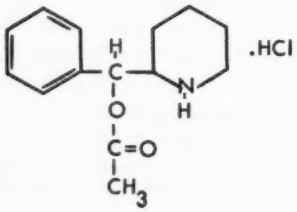


micoren — 0.1ml (15mg of base)

N–crotonyl–α–ethyl-aminobutyric acid dimethylamide



N–crotonyl–α–propylaminobutyric acid dimethylamide



RP8228 — 1.0

1–phenyl–1–(2′–piperidyl)–1–acetoxy methane

Cross-over experiments were carried out with each of the analeptic drugs on groups of ten mongrel dogs that were of comparable size and age. The tests were done at four weekly intervals. The method employed was exactly the same as reported in the preceding cross-over experiments with LSD-25[20].

RESULTS

A summary of the analysed data from each of the six series of experiments are shown in *Table* 2. With every drug that was studied it was observed that the apnœa induced by the rapid injection of thiopentone was immediately and effectively reversed as soon as the analeptic drug was injected.

d'Amphetamine: 0.1mg/kg reduced the recovery time from thiopentone anæsthesia by 25 per cent and the time for ambulation was reduced by 31 per cent. The difference observed with d'amphetamine was highly significant ($p < .001$).

Bemigride and amiphenazole: 5mg/kg of each reduced the recovery time from thiopentone anæsthesia by 19 per cent and the time for ambulation was reduced by 13 per cent. The difference observed was just significant ($p < .04$).

Methylphenidylacetate: 1mg/kg reduced the recovery time from

Table 2

Summary of data showing the effect of analeptic drugs on thiopentone narcosis in dogs

DRUGS TESTED	DOSAGE	RECOVERY TIME HEAD UP MEAN*	S.D.	RECOVERY TIME LEGS UP MEAN*	S.D.	SIGNIFICANCE
		minutes		minutes		
Thiopentone	25mg/kg	69	±11	83	±10	$p < .001$
Thiopentone + d'amphetamine	+o0.1mg/kg	52	14	58	15	
Thiopentone	25mg/kg	57	21	67	19	$p < .04$
Thiopentone + bemigride + amiphenazole	+5mg/kg(each)	46	17	58	18	
Thiopentone	25mg/kg	71	23	104	36	$p < .01$
Thiopentone + methylphenidylacetate	+1mg/kg	60	22	79	29	
Thiopentone	25mg/kg	79	14	88	14	$p < .01$
Thiopentone + iproniazid	+25mg/kg	66	16	77	15	
Thiopentone	25mg/kg	73	24	84	23	$p < .001$
Thiopentone + micoren	+0.1ml/kg (15mg of base/kg)	60	17	67	17	
Thiopentone	25mg/kg	60	26	84	35	$p < .01$
Thiopentone + RP8228	+1mg/kg	42	13	59	19	

*Each mean time represents 20 administrations of thiopentone alone or with analeptic

thiopentone anæsthesia by 15 per cent and the time for ambulation was reduced by 24 per cent. The difference observed with methylphenidylacetate was significant ($p < .01$).

Iproniazid: 25ml/kg reduced the recovery time from thiopentone anæsthesia by 16 per cent and the time for ambulation was reduced by 13 per cent. The difference observed with iproniazid was significant ($p < .01$).

Micoren*: 0.1mg/kg reduced the recovery time from thiopentone anæsthesia by 18 per cent and the time for ambulation was reduced by 20 per cent. The difference observed with prethcamid was highly significant ($p < .001$).

RP8228: 1mg/kg reduced the recovery time from thiopentone anæsthesia by 30 per cent and the time for ambulation was also reduced by 30 per cent. The difference observed with RP8228 was highly significant ($p < .01$).

DISCUSSION

There is a continuous and restless quest for new drugs in therapeutic medicine. This is true also in the field of anæsthetics, because we still lack the fine control that is desirable in the administration of poisonous substances.

*Each ml of solution contains 150mg of combined base

One of the most difficult classes of drugs to control are the intravenous barbiturates, because it is impossible to retrieve that which has been administered, and there are no chemical substances that can be administered to neutralise them in the blood stream. Even though many clinicians prefer not to use drugs in the treatment of barbiturate overdosage or poisoning, we should continue to seek those which will stimulate and support the vital functions that are most seriously depressed and which might shorten the recovery period without producing undesirable side effects[30].

Clinical evaluation in the human is, of course, the ultimate test of efficacy of supportive drugs, but the evaluation of such drugs on a reliable and valid basis of comparison is very difficult and complex[31]. In order to make the initial selection from a group of substances, a comparative study in dogs usually provides suitable objective information.

On the basis of the cross-over experiments carried out on dogs, it was evident that these animals did not develop tolerance or cumulation to a dose of thiopentone which was sufficient to provide anæsthesia for approximately sixty minutes. These studies also showed that the dose of analeptic selected in each case produced an immediate stimulation of respiration which promptly restored breathing after thiopentone apnoea. It was of interest also that *none* of the animals developed any signs of obstructive breathing during the course of the 240 individual experiments, whether they received thiopentone alone or with an analeptic.

The data from these studies should not be the only criterion for selecting the drugs which will prove best in man, because they all appeared to have an analeptic action which was predictable. Micoren and RP8228 both deserve extensive trial, for they are not only effective in the dose tested, but have a high therapeutic index.

SUMMARY

Six series of cross-over experiments were carried out to test the analeptic effect of three new drugs and three recently introduced drugs as compared to that of d'amphetamine. It was found that all the drugs tested had a predictable analeptic effect against thiopentone narcosis in the dosage selected, and it was suggested that micoren and RP8228 deserve extensive clinical trial to determine whether they have a higher therapeutic index in man than the combination of bemigride with amiphenazole or methylphenidylacetate.

Acknowledgements

I am indebted to Mr Stan Meakin, Mr B. St. Germaine and Mr Ronald Welgan of the Medical Research Laboratory, University of Saskatchewan for their very

helpful technical assistance during these experiments. The following pharmaceutical firms kindly supplied the analeptic drugs tested in this study: Abbott Laboratories, Ltd., Montreal (megimide and daptazole); Ciba Company, Limited, Montreal (ritalin); Hoffmann La Roche, Limited, Montreal (marsilid); Geigy Pharmaceuticals, Montreal (micoren); Poulenc Limited, Montreal (RP8228).

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Induced hypotension and post-operative bleeding

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Since the introduction of hypotensive techniques in anæsthesia numerous reports have testified to its efficacy in reducing bleeding at operation.[4 5 12] Confirmation of these impressions has been obtained by the measurement of blood loss at operation in controlled series[10 11].

It soon became clear however that the method was not without its complications and in an endeavour to assess these a questionnaire was circulated to anæsthetists in the British Isles and the United States of America[6 7]. The commonest complication was found to be reactionary hæmorrhage and it was noted that it had occurred 243 times in 27,930 cases and these moreover comprised over 25 per cent of the total complications. It was also the cause of death in eight of the ninety-six deaths reported.

Opinions regarding the responsibility of induced hypotension for post-operative bleeding have however varied. Shackleton[13] commented that post-operative hæmorrhage after hypotensive anæsthesia was rare. Anderson and McKissock[1] reviewed a series of fifty-two major craniotomies operated upon under induced hypotension. There were two cases of post-operative hæmorrhage and it was considered that the incidence was not high. Kern[9] reported a 2 per cent incidence of post-operative hæmorrhage in 600 orthopædic cases and stated that this was certainly no higher than would be expected in a similar series without induced hypotension.

On the other hand Cox[3] thought that his series of prostatectomies showed a slight increase in the incidence of late hæmorrhage and Clark, Bennett and Flautt[2] reporting an incidence of over 5 per cent commented that 'the most significant complication encountered was post-operative bleeding'.

In none of these series was any comparison available with a control group in which induced hypotension had not been used.

Holmes[8] in reference to a series of orthopædic cases in which the incidence of 'reactionary bleeding which required replacement of

blood' was 3 per cent, sums up the position thus: 'Some surgeons have gained the impression that the incidence of post-operative hæmatoma has been higher in this series than after similar procedures performed without ganglionic blockade. However, accurate records of this complication in a control series are not available and reliable comparison is, therefore, not possible'.

No such series indeed appears to have been described in the literature.

A CONTROLLED STUDY OF POST-OPERATIVE HÆMORRHAGE

The opportunity for such a study was provided by a series of thoracotomies carried out in the thoracic unit at the City Hospital, Edinburgh.

The series consists of 381 major thoracotomies carried out for pulmonary tuberculosis in 363 patients. The operations undertaken were lobectomy, segmental resection and decortication and in all cases the pleural cavity was drained into a water-seal bottle. This provided an accurate means of measuring post-operative blood loss, while a routine post-operative chest X-ray revealed those cases in which significant bleeding into the pleural cavity occurred without a corresponding drainage into the bottle.

In 268 of the 381 operations a hypotensive agent was used (hexamethonium, trimetaphan or phenactropinium) and the remaining 113 in which this method was not used form the control group.

CRITERIA OF HÆMORRHAGE

A recorded drainage into the water-seal bottle of 30oz (840ml) or over in the first forty-eight hours after operation was taken as an arbitrary criterion of significant post-operative hæmorrhage for the purposes of comparison between the two groups. In six cases other criteria were used. In two of these (cases 5 and 24) the drainage was known to exceed 20oz (560ml), a post-operative X-ray showed an opaque hemithorax and hypotension was present. One of these cases (case 24) later required thoracotomy for evacuation of the hæmothorax. This was also required in case 18 and was considered a valid criterion of significant hæmorrhage. In cases 13, 15 and 36 the amount of drainage was not recorded. Cases 13 and 36 each required blood transfusion of over two litres post-operatively and case 15 required a further thoracotomy to control the hæmorrhage.

RESULTS

There were thirty-nine cases of significant post-operative hæmorrhage

as defined above. These are listed in TABLE 1. Twenty-eight of these cases occurred in the group in which induced hypotension was used and eleven in the control group.

Table 1

NO	SEX	AGE	TYPE OF OPERATION	HYPOTENSIVE AGENT	INDICATION OF HÆMORRHAGE DRAINAGE OZ	OPAQUE HEMITHORAX	HYPOTENSION	OTHERS
1	M	30	S	T	50		x	
2	M	51	La	H	50			
3	M	31	La	T	40+		x	
4	F	21	LSa	H	32			
5	F	21	L	H	20+	x	x	
6	F	28	LSa	T	38			
7	F	24	L	T	32			
8	F	16	S	H	53			
9	M	39	La	H	40			
10	M	55	Sa	T	80			
11	M	52	L	H	40			
12	F	26	S	T	40			
13	F	23	D	H	—			Transfusion
14	M	24	S	H	57y			Thoracotomy
15	F	48	L	T	—			
16	M	51	D	H	48			
17	F	38	S	P	30			
18	M	42	S	T	—	x		Evacuation
19	F	27	La	H	30			
20	F	48	S	T	32			
21	M	50	S	T	76		x	
22	M	39	D	T	35			
23	F	25	S	H	32			
24	M	48	S	P	20+	x	x	Evacuation
25	M	47	LS	P	38y	x		Evacuation
26	F	23	S	T	38		x	
27	F	36	D	P	32			
28	M	33	LS	P	35			
29	F	38	LSa	—	40			
30	M	22	S	—	30			
31	M	26	L	—	52			
32	F	18	SD	—	30			
33	F	27	S	—	31			
34	F	47	S	—	40			
35	M	30	Sa	—	40			
36	F	45	LSa	—	—		x	Transfusion
37	M	46	S	—	30			
38	F	22	D	—	57		x	
39	M	47	Db	—	30			

Abreviations

Type of Operation:
L = lobectomy
S = segmental resection
D = decortication
a = operation carried out under a previous thoracoplasty
b = operation for evacuation of a clotted hæmothorax

Hypotensive Agent:
H = hexamethonium
T = trimetaphan
P = phenactropinium

y = Amount measured at end of a 72 hour period

The incidence of post-operative hæmorrhage in the whole series is therefore 10.2 per cent. The incidence in the group in which induced hypotension was used was 10.4 per cent and that in the control group 9.7 per cent (TABLE 2).

Table 2

	SIGNIFICANT HÆMORRHAGE	NO SIGNIFICANT HÆMORRHAGE	TOTAL NO OF CASES	INCIDENCE OF HÆMORRHAGE (PER CENT)
Cases with hypotension	28	240	268	10.4
Cases without hypotension	11	102	113	9.7
TOTALS	39	342	381	10.2

DISCUSSION

It is clear from above figures that there is no significant difference in the incidence of post-operative hæmorrhage between the two groups. The figure given for the overall incidence (10.2 per cent) has no intrinsic significance in view of the arbitrary nature of the criteria.

It is perhaps worth noting that all the cases developing serious complications as a result of post-operative bleeding *i.e.* those requiring thoracotomy for evacuation of hæmothorax or to arrest hæmorrhage, were in the group in which hypotension was used. However, the number of such cases is so small that it is difficult to be certain of their significance.

One must, therefore, conclude that there is no evidence in this series that the risk of post-operative bleeding is increased as a result of the use of induced hypotension.

SUMMARY

An attempt is made to determine the risk of post-operative bleeding after anæsthesia with induced hypotension by means of a controlled series of thoracotomies in which post-operative blood loss was measured.

It was concluded that there was no evidence that the use of induced hypotension increased that risk.

Acknowledgements

I wish to thank Mr Andrew Logan, thoracic surgeon, for his encouragement in this work and for permission to refer to these cases. I also wish to thank the staff of the Department of Anæsthetics for permission to quote from their records.

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Trimeprazine tartrate

in pædiatric premedication

A preliminary communication

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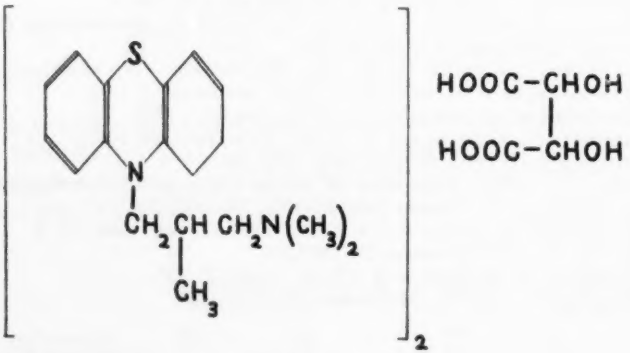
This paper is a report on the use of trimeprazine tartrate as a premedication in children between the ages of sixteen months and twelve years. It has been used as a premedication in a wide variety of operations. In the majority of cases it has been used for ear, nose and throat procedures[1]. So far it has been given to about 150 patients.

PHARMACOLOGY[2]

Trimeprazine tartrate is a phenothiazine derivative and is DL–10-(3–dimethylamino–2–methylpropyl) phenothiazine neutral tartrate. It has the following structural formula.



It is an almost odourless powder which is nearly white and discolours on exposure to light. It is very soluble in water. The pH of a 1 per cent aqueous solution is approximately 6.0.

Trimeprazine has an antihistaminic action as great as promethazine. It has an anti-emetic action greater than that of promethazine, but less than that of chlorpromazine.

Administered intravenously in dogs it causes a transitory tachycardia. In this trial trimeprazine has not been given intravenously, but by mouth it has had no definite effect on the pulse rate.

Trimeprazine was found to have no effect on the blood pressure in rats although chlorpromazine lowered the blood pressure.

Trimeprazine has only a weak anti-adrenaline action. It has a stronger spasmolytic action than chlorpromazine.

In small animals trimeprazine causes general depression, but less marked than chlorpromazine. Trimeprazine potentiates the anæsthetic drugs, but to a lesser extent than chlorpromazine.

Toxic effects

In animal experiments, trimeprazine was not found to cause any liver or kidney damage or to produce any change in the blood picture. Large doses produced death by respiratory depression.

PREMEDICATION – METHODS OF USE

The preparation used was vallergan forte. This is a syrup containing 6mg of trimeprazine tartrate per ml. The syrup was given by mouth one to two hours before operation.

Most patients were given 0.6mg of atropine by injection one hour before operation. Others were given 0.2mg of scopolamine one hour before operation by injection.

With the object of avoiding an injection, the contents of an ampoule containing 0.6mg of atropine or 0.4mg of scopolamine were added to the trimeprazine and the two drugs given together orally. No difficulty was found in getting the children to take either the trimeprazine or the trimeprazine with the added atropine or scopolamine.

The dosage used was 1 – 2mg of trimeprazine tartrate per pound body weight. Most children were given 1.5mg per pound. During one operating session each week, the children were premedicated with atropine only.

DISCUSSION OF RESULTS

Nearly all the children given trimeprazine went to sleep in the ward after a period of half an hour or more. Although being awakened by the injection of atropine or scopolamine, they quickly went to sleep

again. They were often awakened again when moved on to the trolley to be taken to the theatre. Some would go to sleep again if left in the anæsthetic room for a few minutes. However, many of the children were awake for the induction. The majority of these were sleepy and were co-operative and amenable.

After the first few occasions in which trimeprazine was used it was found to be more effective if the drug was given two hours or more before operation. It was of less value if given an hour or less pre-operatively.

Most of the children in the ENT theatre were anæsthetised with nitrous oxide–oxygen and ether or thiopentone and suxamethonium and narcosis maintained on nitrous oxide–oxygen and ether or halothane.

Since trimeprazine is a phenothiazine derivative, we were concerned that the children would not remain anæsthetised for a longer period of time than normal. This in fact did not occur. The children quickly regained their cough and swallowing reflex. The majority of children spat out their airways within twenty minutes of returning to the ward. Thereafter they would remain asleep for several hours, but at all times easily rouseable. They did not appear pale as patients who have been given chlorpromazine sometimes do.

It seemed to be a suitable premedication for those children who underwent guillotine tonsillectomy, but this is not a common procedure at this hospital.

Until this trial began, papaveretum and scopolamine had been the standard premedication. There was a considerable reduction in the amount of vomiting when trimeprazine began to be used.

The nursing staff were satisfied with the drug as a premedication and thought that the post-operative course was good in that the children vomited less and were quieter. When scopolamine was substituted for atropine in the premedication with trimeprazine, the children were found to be more sleepy and a greater number actually asleep during induction.

Where it is felt that the children should be more sleepy before operation, trimeprazine and scopolamine are to be preferred. One advantage of using scopolamine is that it has a definite amnesic effect.

It was interesting to note that the children given scopolamine had lower pulse rates than those given atropine.

With the object of avoiding an injection before operation, some children were given atropine or scopolamine by mouth. The oral route of administration is not so effective or reliable as giving the atropine or scopolamine by injection. In a few cases the children salivated. But even in the cases in which the secretions were most

pronounced, the administration of the anæsthetic was not affected apart from sucking out the pharyngeal secretions during induction. This was only necessary in a very few cases.

The last thirty children undergoing ear, nose and throat operations have been given trimeprazine 1.5mg per pound body weight and 0.4mg of scopolamine by mouth two hours before operation. This has provided a satisfactory premedication in most cases and no injections have been given.

Trimeprazine with or without scopolamine has also been used to sedate children undergoing various procedures without a general anæsthetic. So far it has proved useful in such cases.

Table 1

Tabulated results of ENT cases

	ATROPINE 16 CASES	PAPAVERET AND SCOP. 15 CASES	TRIMEPRAZ AND ATROP. 67 CASES	TRIMEPRAZ AND SCOP. 46 CASES
Condition of child on induction				
Apprehensive	12 (75%)		17 (25%)	8 (17%)
Amenable to induction	4 (25%)		42 (63%)	21 (46%)
Asleep	nil		8 (12%)	17 (37%)
Post-operative recovery				
Length of time airway remained in child's mouth				
0–20 minutes	14 (88%)	7 (47%)	54 (80.5%)	36 (78%)
20–40 minutes	2 (12%)	5 (33%)	12 (18%)	7 (15%)
40–60 minutes	nil	3 (20%)	1 (1.5%)	3 (7%)
Vomiting				
No vomiting	4 (25%)	2 (13%)	39 (58%)	27 (58%)
1–2 vomits	10 (63%)	6 (40%)	19 (28%)	17 (37%)
Over 3 vomits	2 (12%)	7 (47%)	9 (14%)	2 (4%)
Post-operative sedation				
Children given no sedation	11 (69%)	13 (86.5%)	52 (77.5%)	34 (74%)
Children given nepenthe	5 (31%)	2 (13.5%)	15 (22.5%)	12 (26%)

CONCLUSIONS

Trimeprazine has an hypnotic and calming effect on the children. There was a definite difference between those children who were premedicated with atropine and those with trimeprazine. Most of the children were either asleep in the anæsthetic room or amenable to induction.

To obtain the best results, the trimeprazine should be given at least two hours before operation.

Children who had had trimeprazine as a premedication vomited less than those who had atropine only or papaveretum and scopolamine.

Children given trimeprazine and scopolamine were more sleepy than those given trimeprazine and atropine.

It is felt that trimeprazine tartrate is a drug that is worth further investigation.

Acknowledgements

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Anæsthesia for intracardiac surgery

using cardiopulmonary bypass

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The following is an account of the anæsthetic routine used for twenty cases of open cardiac surgery at the Queen Elizabeth Hospital, Birmingham. The types of lesion corrected included ventricular septal defects, atrial septal defects, Fallot's tetralogy and pulmonary stenosis and the ages ranged from eight months to eleven years. Most of these children were undersized, with exercise limitation in varying degrees, and had histories of frequent respiratory infections. On examination they could be divided into three groups: those who were permanently cyanosed, as in the Fallot's; those cyanosed only on exertion; those never cyanosed.

The children were admitted with diagnosed intracardiac lesions for operation, the preliminary clinical examinations and investigations such as angiocardiography and cardiac catheterisation, having been performed previously.

The operations were performed using the Lillehei-DeWall bubble pump oxygenator[1], and with continuous electrocardiogram and electroencephalogram monitoring.

THE MACHINE

In order to produce satisfactory conditions for intracardiac operations it is necessary in some way, to bypass the heart and lungs and also to produce cardiac arrest. Therefore, a means of maintaining a circulation of blood to the vital structures, *eg* brain, spinal cord and kidneys, and a means of oxygenating that blood are necessary.

CARDIAC ARREST

It has been found by Glenn *et al*[2] that the heart itself normally has a blood supply of 44–66ml per minute per 100g cardiac weight or 3.3–6.7 per cent of the total cardiac output. Bing[3], however, showed

that the heart when beating empty, requires only 20–30 per cent of this amount; *ie* 70–80 per cent of the oxygen consumption of the normal heart is concerned with external work. Also if the heart is arrested, then its oxygen requirements are minimal. Bentall[4] observed that the amount of lactic acid formed during arrest was less than one-third that formed by the beating ischæmic heart. Melrose *et al*[5] showed that coronary arrest for short periods was compatible with the return of normal cardiac function when the coronary circulation was restored and Gerbode and Melrose[6] stated that elective cardiac arrest is a safe adjunct to open heart surgery. Coronary arrest, together with cardiac arrest, greatly diminishes the flow of blood into the heart from the coronary sinus, leaving a much drier field for the surgeon. The only blood entering the heart, during bypass, being from the bronchial arteries by way of the pulmonary veins. This latter, however, is easily dealt with by the surgeon's sucker, in most cases being less than 1.25 per cent of the total cardiac output[7] and only being troublesome in Fallot's or chronic respiratory conditions where the bronchial circulation is large. The heart, therefore, can be bypassed by draining its venous inflow, namely, the superior and inferior vena cavæ, by means of cannulæ into these vessels. The coronary circulation is stopped by a clamp on the aorta and the heart itself is arrested by injecting potassium citrate into the aorta proximal to this clamp[5].

CIRCULATION

Circulation to the rest of the body is carried out by means of a pump. The venous blood from the patient is passed, by gravity, from cannulæ in the venæ cavæ, to a venous well situated below the level of the table. Thence it passes through a venous pump of the Sigmamotor type to the oxygenator and then through an arterial filter and second Sigmamotor pump into an artery in the body, usually the femoral. The tissues are, therefore, supplied by blood which passes in a retrograde direction from the femoral artery to the aorta. The perfusion rate is usually calculated to give 2.4 litres of blood per square metre body surface. As the weight of the patient is known, the arterial pump is set to measure by means of a stop watch, the rate of pumping 5 per cent dextrose into a graduated bottle. The venous pump is set at approximately the same rate, but is altered during perfusion if the venous and cardiotomy returns vary.

OXYGENATION

Venous blood and oxygen are passed into the lower end of a vertical tube at a rate of 3 litres of oxygen per 1 litre of blood. In this way, the

blood comes into contact with the oxygen and is carried to the upper end of the tube as a mass of foaming bubbles. In this oxygenator the blood becomes 95–98 per cent saturated with oxygen and carbon dioxide is freely given off. Stokes and Gibbon[8] showed that when oxygen only was used in the oxygenator marked carbon dioxide washout and respiratory alkalosis were produced. Callaghan *et al*[9] showed that the low carbon dioxide, due to the efficiency of the oxygenator, compensated for the metabolic acidosis and fall of bicarbonate which occur during bypass. Mendelsohn *et al*[10] attributed signs of temporary impairment of the central nervous system—a delay in recovery from anæsthesia and low tolerance to anæsthesia following the bypass run, to the low carbon dioxide level in the blood and added carbon dioxide to the oxygenator during bypass. Scurr[11], using 100 per cent oxygen had no evidence of carbon dioxide lack. DeWall *et al*[12] also had no deleterious effects using only oxygen.

ANÆSTHETIC ROUTINE

Anæsthetic requirements

These are a prolonged light anæsthetic with rapid return of consciousness. The induction should be smooth and quiet, so avoiding breath holding and crying which may cause subsequent cyanosis and cardiac strain. The agents used should be non-toxic to the tissues generally and the heart in particular, and should not produce fluctuations in heart rate or blood pressure. Respiration is best 'controlled' to ensure adequate ventilation and a controllable field for the surgeon.

Premedication

Most of these children have been in hospital many times before, both for the treatment of respiratory infections and for investigations such as cardiac catheterisation and angiocardiography and have become 'allergic' to needles of any sort. In addition, many of them, particularly in the younger age groups, have few suitable veins, so that intravenous induction cannot be the smooth procedure desired. It seems ideal, therefore, to have the child brought to the theatre asleep. For this purpose we use rectal thiopentone, 50mg per kilo body weight, given half an hour pre-operatively. Keown *et al*[13] used intramuscular thiobarbiturates with hyalase to produce sleep. One of their objections to the rectal route being the occasional return of the solution by the child. To obviate this, we prepare the child for five days pre-operatively, with an early morning enema, followed later by the instillation of 10ml. water. The child is put in a quiet, darkened room and encouraged to sleep. After two to three days of this routine the

child sleeps following the rectal water and on the day of operation, the substitution of thiopentone for the water results in successful retention.

Maintenance of anæsthesia

Telford and Keats[14] state that they have repeatedly observed, that the heart became more amenable to manipulation, when the anæsthetic agent was decreased or eliminated. They pointed out that light general anæsthesia for cardiac surgery had been made possible by the relaxants, hyperventilation and controlled respiration, and by the use of analgesic concentrations of general anæsthetic agents.

They used succinyl choline, plus controlled respiration, plus analgesic doses of ether. Patrick, Theye and Moffitt[15] used cyclopropane for induction and ether plus oxygen for maintenance. Telford and Keats[14] found frequent arrhythmias with cyclopropane, *eg*, bradycardia, premature ventricular contractions and nodal rhythm. Mendelsohn *et al*[10] in a series of thirty-seven patients between the ages of eighteen months and fifteen years, used cyclopropane in thirty cases and ether in seven. They found post-operative respiratory complications were less with cyclopropane than with ether. Auld[16], on the other hand, showed that a failure of circulation was common in children undergoing major surgery under nitrous oxide-oxygen, ether anæsthesia, with or without relaxants.

Using nitrous oxide, oxygen, curare and pethidine he found that children were much better on the table, withstood more extensive surgery and were better post-operatively, than those anæsthetised by other means. Heller *et al*[17] have shown by extensive electrocardiogram studies, that nitrous oxide-oxygen analgesia, plus curare, has little, if any, harmful effect on the cardiac mechanism. In view of the constant use of diathermy by our surgeons we have not used either cyclopropane or ether. With regard to halothane, the reports of observations of its cardiovascular effects, namely, alterations in pulse rate and falls of blood pressure,[18 19 20], have discouraged us from the use of this agent. We, therefore, use a combination of nitrous oxide and oxygen with curare.

Monitoring

Throughout the operation we have continuous electroencephalogram and electrocardiogram monitoring with arterial and venous blood pressure recordings, (FIG. 1). A constant watch is also kept on the body temperature, which tends to fall during bypass.

The arterial blood pressure is recorded in the aorta by a catheter passed through the femoral artery and the venous pressure is taken by means of a catheter into the inferior vena cava via the femoral vein.

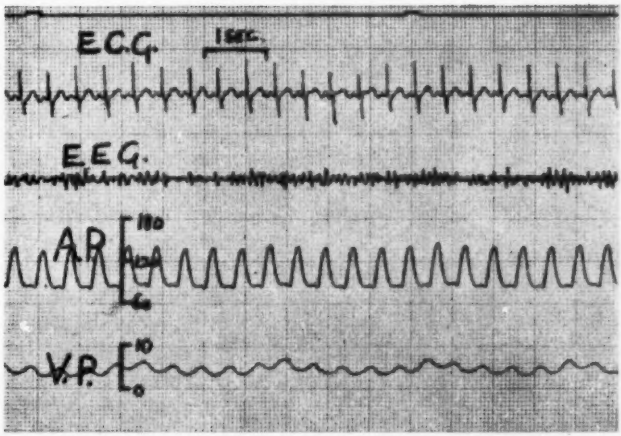

FIG. 1 Chart showing ECG and EEG monitoring and arterial (AP) and venous pressures (VP) during operation

The electroencephalogram is recorded by means of steel pins hammered lightly into the skull. Theye, Patrick and Kirklin[21] found the electroencephalogram a useful monitoring device using scalp electrodes and Owens *et al*[22] concluded that the electroencephalogram is a reliable and sensitive indicator of the adequacy of cerebral perfusion. Scurr[11] stated that the activity of the electroencephalogram is the best index of satisfactory blood flow and cortical viability. Hutton *et al*[23], although finding the electroencephalogram useful, use pupil size and reaction as a guide to cerebral perfusion. Keats *et al*[24], however, did careful observations on changes in pupil size, its reaction to light, and skin colour changes, but found that none of these were consistent enough to be used as a guide for altering perfusion rate. Although we have found the pupil size to be a useful, if inconsistent, guide to cerebral perfusion, to prevent frequent examination of the eyes with possible trauma we have used the electroencephalogram grades as shown. Hudson[25] showed six grades of electroencephalogram (FIG. 2).

With the method of anæsthesia used in our cases, the electroencephalogram is maintained at either grade 1 or 2.

Routine

When asleep, the child is brought to the anæsthetic room, where atropine 0.4 – 0.6mg, depending on size, is given intravenously. This injection is usually easy to give as the veins are well dilated and although the hand is often reflexly moved there is no return of

Grades of E.E.G.—Human

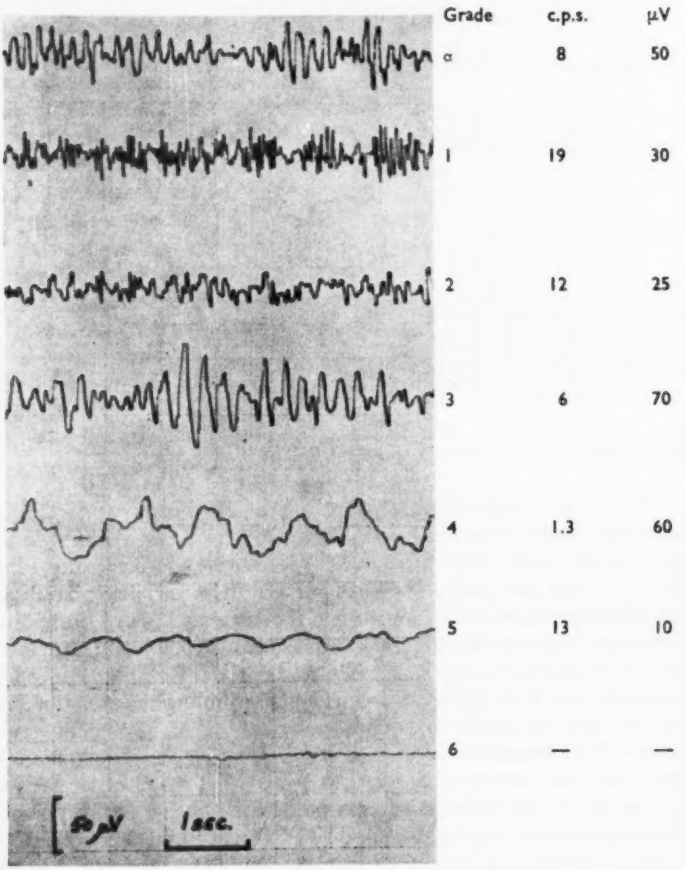

FIG. 2

GRADE α	waking record
GRADES 1 and 2	light anæsthesia
GRADES 3 and 4	moderate depression of cerebral function
GRADES 5 and 6	progressive loss of cortical electrical activity

consciousness. After a few breaths of nitrous oxide-oxygen, d-tubocurarine (0.5mg/kilo) is given intravenously. As apnœa occurs the lungs are inflated with oxygen, and a Magill tube is passed by direct

laryngoscopy into the trachea. We prefer the uncuffed tubes, as the cuff tends to reduce the size of tube which can be passed.

Nitrous oxide with 25 per cent oxygen is administered and respiration is taken over by hyperventilation through soda lime in a Boyle circle absorber. The patient is then weighed and taken into the theatre; the weight before and immediately after operation is noted as a check on blood replacement. The electroencephalogram and electrocardiogram electrodes are now placed in position and an œsophageal thermometer passed. A polythene catheter is inserted into the cephalic vein, and connected, by means of a three way tap, to a bottle of heparinised dextrose. This drip is used for blood replacement, anæsthetic drugs, heparin and protamine. Hæmostasis throughout the operation is meticulous, all swabs being weighed and all blood loss charted. Blood is replaced as it is lost, keeping 20–50ml in advance. In order to give small measured amounts of blood by syringe, we have devised the stand shown in FIGURE 3 which allows the bottle of blood to be tilted.

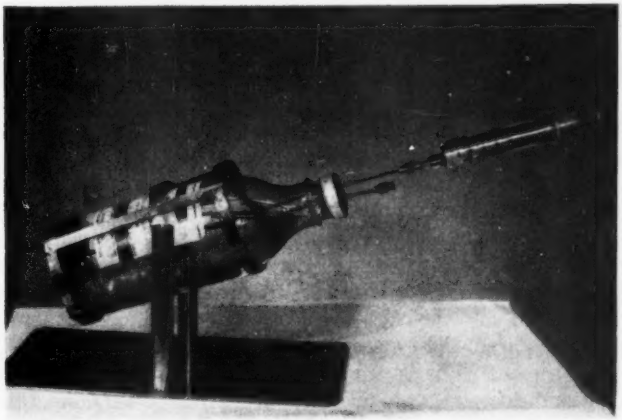

FIG. 3

The two surgical teams now commence the sternal split thoracotomy and the femoral cannulations. Heparin, 3mg/kilo body weight is given prior to the cannulations. Polythene catheters are passed, via the right femoral artery and vein, into the aorta and inferior vena cava respectively, for blood pressure readings. The left femoral artery is cannulated for connection to the arterial side of the pump and the superior and inferior vena cavæ are cannulated for connection to the venous side of the pump. The pump is switched on, the patient

now being on partial bypass. When tapes round the vena cavæ are tightened, all venous flow is directed to the pump and the heart and lungs are totally bypassed. A perfusion rate of 2.4 litres/square metre body surface is aimed at. If this is not adequate to maintain cerebral circulation, as shown by the electroencephalogram, adjustments must be made to bring the electroencephalogram back to grades 1 or 2, as before. We have not found it necessary to use vasopressors, such as l-noradrenaline during bypass[23]. During cardiac bypass, the coronary arteries are filled by retrograde flow from the aorta. The aorta is then clamped, and potassium citrate injected proximally (2ml of 25 per cent potassium citrate are added to 18ml heparinised blood and just enough is given to produce cardiac arrest). Once the heart is arrested, ventriculotomy is rapidly performed, to prevent stretching of the flaccid cardiac muscle[26]. Due to dilution of anæsthetic drugs in the oxygenator pump blood during bypass, the anæsthesia usually lightens, the child may start to move the eyes or limbs and diaphragmatic movements may interfere with the surgeon. We, therefore, give additional doses of curare (0.2mg/kilo) prior to total bypass.[23 24] If this is insufficient, we give further doses of curare (0.2mg/kilo) and thiopentone (1.5mg/kilo) directly into the pump. During perfusion the lungs are held motionless, but partially expanded with oxygen.

When the intracardiac surgery has been completed, the aortic clamp is released and restoration of the cardiac action results from the washing out of the potassium citrate from the coronary arteries. When the heart is beating satisfactorily, the ventricle is closed and protamine sulphate (5mg per 3mg heparin) is given slowly to bring the clotting time back to normal. The vena caval and femoral cannulæ and catheters are removed, hæmostasis is secured, blood loss made up if required, and the chest is closed. Atropine and prostigmine are given as required. Pharyngeal and tracheal toilet is performed, and the endotracheal tube is removed. The child is usually awake and talking as the dressings are being applied. After re-weighing, the child is put into bed, and sent back to the ward, breathing oxygen from a polythene mask.

SUMMARY

An account of the anæsthetic technique, and type of pump oxygenator used, in a series of twenty cases of open cardiac surgery is given.

The problems of premedication and choice of anæsthetic are discussed.

Acknowledgements

I wish to acknowledge my thanks to Dr Murtagh for his valuable criticism and

advice. I am also very grateful to Mr L. D. Abrams and Dr W. A. Hudson for their helpful advice and guidance. I am indebted to Mr T. F. Dee for the photographs.

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Summary of the Sixth Lister Memorial Lecture

The Sixth Lister Memorial Lecture was delivered by *Dr Nathan B. Eddy* in Adam House, Edinburgh on 1 October 1959. The lecture, which was endowed some years ago by J. F. Macfarlan & Co. Ltd and T. & H. Smith Ltd, is under the auspices of the Society of Chemical Industry. Dr Eddy is Chief of the Section on Analgesics at the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland and Secretary to the Committee on Drug Addiction and Narcotics of the National Research Council.

In his lecture **THE CHEMICAL STRUCTURE AND ACTION OF MORPHINE-LIKE ANALGESICS AND RELATED SUBSTANCES** Dr Eddy traced developments based on his own experience in co-operation with chemists, pharmacologists and medical workers on analgesic drugs. Dr Eddy defined the main structural requirements of the morphine-like analgesics and methods by which greater specificity of action could be secured. He described the properties of the benzomorphan derivative, known as NIH 7519, or phenazocine, in which a marked separation of analgesic activity and liability to produce addiction had been secured. Although this separation was particularly striking in monkeys, the effect persisted to a modified degree in man and the drug should find a useful place in medical practice. Other powerful analgesics having reduced side effects were also likely to become available in the future.

Summary of symposium on recent advances in analgesia

A symposium was organised on 2 October 1959 by Duncan, Flockhart & Co. Ltd. It was held in B M A House, Edinburgh and the chair was taken by Professor D. M. Dunlop, Professor of Therapeutics in the University of Edinburgh.

The morning session was devoted to five short papers on aspects of analgesia.

Dr D. A. Cahal, Lecturer, Department of Pharmacology, University of Leeds, spoke on SCREENING OF ANALGESICS IN MAN.

Dr Cahal began by outlining the background of analgesic testing in normal man. He pointed out the differences between such testing in animals and man and suggested that, in spite of many views to the contrary, the results in man might be at least as valuable as those obtained in animals.

The especial value of tests in man was as a preliminary to clinical trial in patients. Clinical trials of analgesics were always difficult to conduct owing to the small number of patients with the necessary features of severe, constant pain and a reasonable level of intelligence. These difficulties were much increased when the dose to be used in the trial had to be derived from results obtained in animals. The use of the wrong dose levels might lead to an erroneous conclusion or discontinuation of the trial because of side effects. Detection of the latter and the dose level at which they occur were important advantages of preclinical investigations in man.

Dr Cahal then described his technique for estimating elevation in the threshold of pain produced by muscular ischaemia in the forearm. It was important to keep the experiments as simple as posssible.

Discussion

Dr C. G. Haining (Edinburgh) asked if any correlation had been found between the dose response curve in man and that in animals.

Dr Cahal considered that there was little or no correlation. Animal studies of analgesics were almost useless for the purpose of predicting effects in man.

Dr Harris Isbell (Addiction Research Centre, Lexington) asked at what intervals readings were made in volunteers and whether the

development of muscle soreness was a problem. He had found this to be so when attempting to develop a technique similar to Dr. Cahal's.

Dr Cahal replied that initially he had had this experience also. By making readings not oftener than once an hour muscle soreness could be avoided.

Professor R. B. Hunter (Dundee) asked about the significance of detecting side effects in the course of experiments in volunteers.

Dr Cahal stressed that this was a most useful feature of this type of experiment as it made it possible to specify the side effects to be looked for in a subsequent clinical trial. In addition, doses could be selected at which the optimum ratio of analgesic effect to side effects was obtained.

Professor Stanley Alstead (Glasgow) asked whether Dr Cahal had observed any difference in the response of his subjects which could be related to their personality or physique.

Dr Cahal replied that he had not been able to find any correlation of this type.

Dr Mark Swerdlow (Consultant Anæsthetist to Salford Hospital Group) discussed **ANALGESIC TESTING DURING GENERAL ANÆSTHESIA.**

The use of a lightly anæsthetised patient undergoing an operation as a subject in whom to test analgesics might eliminate some of the unpredictable factors inseparable from trials in conscious patients or volunteers. Anæsthetised patients reacted in various ways to the painful stimuli inflicted by the surgeon and it was possible by comparing the effectiveness of various drugs in abolishing these responses to arrive at a ratio between the analgesic potencies of these drugs. Dr Swerdlow outlined his technique and indicated the variables which might affect results in anæsthetised patients. He emphasised the necessity of using a standard anæsthetic technique for all cases.

Discussion

Dr Nathan B. Eddy (National Institutes of Health, Bethesda) asked how the relative potencies found with Dr Swerdlow's and Dr Cahal's methods compared with those found by clinical trial in conscious patients.

Drs Swerdlow and Cahal considered that their results corresponded very closely with those found in clinical trials.

Dr A. R. Hunter (Manchester) described experiments he had carried out to compare the effects of certain analgesic drugs on the respiration of anæsthetised patients and conscious animals. He had found correlation between analgesic and respiratory depressant activity in both man and animals.

Dr J. W. Dundee (Director of Department of Anæsthetics, Belfast) talked on **ANALGESIC PROBLEMS IN AMBULANT PATIENTS.**

Most of the reported work on the relief of intractable pain dealt with its management in hospital by neurosurgery, nerve-block, or analgesic drugs; the latter had usually been given parenterally. Most patients with intractable pain are, however, treated at home and orally administered analgesics are preferable. In Liverpool and more recently in Belfast, an outpatient clinic had been run specifically for patients with chronic pain. The methods used for relief of pain were nerve-block and orally administered analgesics; the latter were required in 52 to 54 per cent of patients. A simple system had been developed for evaluating the analgesics used, which took into account both analgesic activity and the incidence of side effects. It was possible by this simple method to show significant differences in the effects of varying doses of analgesics and to select an optimum dose. This usually corresponded closely to that found by other techniques. Placebos had been found to give relief to only 16 per cent of patients with pain of organic origin. Of patients complaining of pain for which no organic cause could be found, however, 48 per cent obtained relief from placebos.

Nausea and vomiting were troublesome side effects in ambulant patients and a number of anti-emetic drugs had been found useful. Vomiting was easier to control than nausea.

Addiction to analgesic drugs had not been found to be a problem in these patients.

Discussion

Professor D. M. Dunlop (Edinburgh) commented that any encouragement to pharmaceutical manufacturers to make mixtures of potent drugs was to be deprecated. Patients were not all alike in their requirements for the various ingredients and there were already far too many such preparations on the market.

Dr Dundee agreed that this was so, but felt that it was difficult for the average patient to remember which tablets he had to take and at what time and that such mixtures provided the best solution until ideal analgesics became available.

Dr B. R. Simpson (Oxford) described the use of large doses of morphine with amiphenazole in post-operative pain. It had proved possible to restore patients' vital capacity to 95 per cent of normal shortly after recovery from the anæsthetic.

Dr S. G. de Clive-Lowe (Senior Anæsthetist, St. Luke's Hospital, Guildford) described his work on **GENERAL ANALGESIA WITH LOCAL ANALGESICS.**

The intravenous administration of lignocaine during operation under general anæsthetics had been found to provide useful post-operative analgesia in a large proportion of patients. In a series of 1000 cases who received lignocaine by intravenous infusion, 77 per cent had a period of post-operative analgesia and 25 per cent had analgesia for ten hours or more. In a second series of four hundred patients who received lignocaine by intermittent intravenous injection, 89 per cent had a period of post-operative analgesia, 61 per cent had relief for eight hours or more, and 43.8 per cent for more than eighteen hours.

Dr de Clive-Lowe stressed that although in his hands intravenous lignocaine had been a very safe technique, it was not one to be lightly undertaken and accurate dosage was essential.

Discussion

Professor R. Woolmer (London) described an anæsthetic technique he had observed on a recent visit to South Africa in which procaine was given intravenously in doses up to 4 or 5g in an hour. This usually produced an extreme degree of hypotension. Professor Woolmer wondered to what extent Dr de Clive-Lowe thought that lignocaine was contributing to general anæsthesia in his cases.

Dr de Clive-Lowe replied that he had given intravenous lignocaine to conscious patients and it had caused them to fall asleep, but he did not feel the central effects of lignocaine made a significant contribution to general anæsthesia.

Dr Cahal pointed out that intravenous lignocaine had recently been used in the treatment of status epilepticus, which seemed strange in view of the fact that local analgesics normally produce convulsions in overdosage.

Dr A. H. Beckett (Head of the School of Pharmacy, Chelsea College of Science and Technology) spoke on **STEREOCHEMICAL FEATURES OF ANALGESICS.**

Dr Beckett dealt first with the problems facing the chemist in his attempts to achieve specificity of action in new analgesic compounds. He reminded his audience of the wide difference in activity between isomers both of known analgesics such as morphine, methadone and the morphinans and the new compounds described by Dr Eddy in his Lister Lecture of the previous evening. It was thus clear that a simple rearrangement in space of one or two atoms of a compound could completely alter its pharmacological activity. Certain features of spatial arrangement might be common to potent analgesic compounds and this might provide a logical starting-point in a search for specificity of action. In simple terms, one might consider a molecule of a compound as conforming, in a spatial sense, more or less well to a surface at the receptor; thus isomers which had the relevant groups

arranged so as to correspond to sites on the receptor surface, would be active, while isomers arranged differently would be much less active or even inactive. Morphine and related compounds could be regarded as fitting the receptor at three points. If, in the morphine molecule, the position of these points relative to each other was changed, the compound would not fit so well and so be less active.

Experiments had been carried out to show that molecules of a compound can, under certain conditions, be made to leave 'foot-prints' in silica gel. After the gel had formed in the presence of the compound, it was dried and the compound extracted. It was then found that the dried gel would adsorb isomers of compounds closely related to and having the same configuration as the one which made the foot-prints much more readily than it would adsorb other isomers of the same compounds. By this technique it had been possible to show that l-morphinan might have the same configuration in space as l-morphine itself.

The problem of specificity might, therefore, be considered from the viewpoint of trying to achieve a good fit at the desired receptor, but a poor fit at other receptors where side effects such as respiratory depression might arise.

Dr Beckett then suggested the possible shape of the morphine receptor and indicated how many other potent analgesics could be arranged in space to agree with this concept. There was spectrophotometric and crystallographic evidence to support such a spatial configuration.

This raised the interesting problem of how an analgesic could be converted, by means of a small change in the substituent on the nitrogen, into an antagonist to itself. The change did not produce any alteration in spatial configuration. The explanation was probably in the ease or difficulty of an oxidative de-alkylation occurring at the receptor site.

Dr Beckett ended his paper by discussing how stereochemical considerations might help in the search for potent, specific compounds. Enzymes of various kinds, including those concerned with the penetration of surfaces, were three-dimensional and had stereospecificity and this might be relevant to the design of compounds intended to reach, and act on, one receptor site only. The stereospecificity of enzymes might account for the gross discrepancy between action in animals and man observed with some drugs. Quite minor changes in a molecule might greatly limit its ability to assume different spatial forms without interfering with its fit to the receptor.

Discussion

Dr E. S. Stern (Edinburgh) asked what was the relationship between

ease of oxidative de-alkylation to nor-compounds and analgesic antagonism.

Dr Beckett explained that in his view it was easy formation of nor-compounds at the receptor which gave analgesia.

Dr R. B. Barlow (Edinburgh) raised two points. The first was how it could be explained that increasing the length of the chain attached to the nitrogen first caused a drop and then an increase in activity – as for instance in Dr Eddy's N-phenethyl compounds. The second concerned the idea of the receptor. No-one knew where the analgesic receptor was, and it was, therefore, a little dangerous to postulate the existence of a definite receptor at which analgesics were working. It was, until recently, easy to visualise the appearance of such a receptor, but now the features of the N-substituted nor-compounds made one wonder if there might not be a number of receptors, as otherwise the single receptor seemed to be becoming unduly complicated.

Dr Beckett emphasised that the number of receptors, or their exact appearance, were unimportant in relation to the steric theory of drug action; the important thing was that minor changes in steric configuration could profoundly affect the activity of drugs.

He stressed that his explanation was not necessarily right, but that it offered a solution on which to base drug design.

Dr R. E. Lister (Edinburgh) pointed out that among Dr Eddy's compounds there were a few in which both dextro and lævo isomers were active, although one was more active than the other. He asked how Dr Beckett explained this in terms of the relationship between molecule and receptor surface.

Dr Beckett suggested that this could very well be explained by his theory. He had not claimed that all three points of attachment to the receptor were necessary; two probably were, while the third might facilitate or interfere, depending on its position relative to the other two. Thus compounds which had two groups correctly situated might show activity, but to a lesser degree than those which had three.

In the afternoon, two panel discussions were held, each followed by general discussion.

First panel discussion:	NEW SYNTHETIC ANALGESICS
Dr A. H. Beckett	Dr P. V. Petersen (Lundbeck & Co., Copenhagen)
Dr N. B. Eddy	Dr E. S. Stern (J. F. Macfarlan & Co. Ltd)
Dr R. E. Lister	(J. F. Macfarlan & Co. Ltd)

Dr Beckett discussed the use of various steric factors to hinder a too rapid metabolism of a compound. The reversed esters of

pethidine, for example, are fairly quickly metabolised in man and analgesic activity in man is relatively low compared with that in animals. When steric factors are introduced around the ester group to try and protect this from attack by esterases, relative activity in man approaches that found in animals. The placing of small groups to protect sensitive parts of a molecule seems to offer quite a fruitful approach to the design of more effective molecules.

Dr Eddy described certain aspects of the work which had been done on the benzomorphan series of compounds. It was of particular interest to observe the effect of changing the group attached to nitrogen. Increasing the group from methyl to ethyl, propyl and isobutyl, causes activity to disappear, but it reappears when an amyl group is substituted. In recent work, a group has been inserted near the centre of the molecule, and it has been found that a hydroxyl in this position decreases activity; this is in contrast to the morphine series where activity is increased by this modification.

Dr E. S. Stern said that when he and his colleagues began their work with analgesics in 1953, the only available information on the effect of nitrogen substitution was the original work by Schaumann and Eisleb, who had shown that methyl was the optimum group. As there was no obvious reason for this, it was decided to examine the effect of some basic residues at the nitrogen atom. Two substances which had ether-type groupings showed high potency and it was concluded that this grouping had a specific effect on potency. A variety of other oxygenated groups were tried, but found to lack activity. It was eventually found that in a series of ethoxyalkyl substituted compounds where the alkyl chain is from 2 to 6, potency is high with chains of 2 and 4 carbon atoms, but markedly less with 3, 5 and 6. Replacement of the ethyl group with phenyl or benzyl produced a slight increase in potency, while introduction of a tetrahydrofurfuryl group was found to produce a very marked increase – about seven times over the original compound.

Two of the compounds resulting from this work are at present undergoing clinical trial.

Dr R. E. Lister, describing the pharmacology of two of the compounds described by Dr Stern, pointed out that a gain in potency in an analgesic is of no value if it is accompanied by an equal or greater increase in side effects. It had been shown by Dr Beckett and Dr Eddy that it was possible to effect some separation of analgesic and side effects.

The two compounds which had been examined were potent analgesics with a shorter duration of action than morphine. Their

histamine-liberating effect was considerably less than that of pethidine and this might be of interest in the light of the suggestion by Shaw that the side effects of morphine may in part be due to liberation of histamine. The compounds had failed to produce vomiting in dogs in whom proportionately smaller doses of pethidine had done so.

There would seem, therefore, to be a distinct possibility that many side effects would eventually be dissociated from analgesia.

Dr P. V. Petersen, speaking about the analgesic drug, ketobemidone, stated that it had been in use in Scandinavia for nine years. It had been used principally in combination with a spasmolytic agent, diphenyldimethylaminobutene (A 29) which, in spite of having proved unsatisfactory in clinical trials, had been shown to have a potentiating effect on ketobemidone. At the point when this combined preparation was about to be marketed, it was reported by Isbell that ketobemidone was one of the most addictive drugs known, more potent than morphine in inducing euphoria and relieving abstinence and with an addiction liability as great as that of heroin, and that the drug should not be used clinically.

In spite of this, the clinical potentialities were considered such that it was decided to proceed with marketing. After nine years, during which the combined product has been extensively used, it does not appear to play an important part in the abuse of narcotic drugs in Denmark.

Dr Harris Isbell pointed out that the work on ketobemidone had been done a long time ago and he might not now agree with some of the statements made at that time.

In considering addictiveness, there were two factors to consider. The first was danger. This was very slight in ordinary clinical practice where the drug was properly controlled and understood. But a drug like ketobemidone, with its euphoriant and dependence-producing properties would be very dangerous if it were to become available to individuals with distorted personalities.

Dr Nimb (Copenhagen) stated that ketobemidone given as the combination is less dangerous than the pure substance, as the side effects of the antispasmodic become unpleasant as the dose rises.

Dr Eddy said that in his view the addition of other agents is not effective in preventing abuse, as addicts tend to disregard the unpleasant side effects.

Dr W. T. Simpson (Edinburgh) mentioned a recent finding by Beecher that papaverine appeared to potentiate the analgesic effect of morphine.

Dr Beckett considered that combinations of closely related compounds might provide a means of obtaining greater specificity, by

producing a blocking effect at some of the receptors and preventing the active compound from reaching them.

Dr Cahal stated that he had tried to confirm Beecher's observations on papaverine, but has been unable to repeat his results.

Professor Woolmer asked Dr Beckett if the possibility of protecting sensitive parts of a molecule by steric means might be a way to obtain drugs with prolonged duration of action.

Dr Beckett felt that this was possible, but the biochemistry of many compounds was still unknown and a 'hit-or-miss' approach had often to be adopted. Much more biochemical study of common drugs was called for.

Second panel discussion: **PROBLEMS OF ADDICTION**

Dr Roy Goulding Dr M. Nimb Dr Harris Isbell

Dr Roy Goulding considered that drug addiction might arise as a social habit, as an outcome of economic plight, as a deliberate vice in the psychologically abnormal or as a sequel of therapeutic use.

In this country the taking of drugs does not have social approval and economically there is no need to seek this form of outlet. The criminal form of addiction is a very small problem indeed.

The remaining problem, therefore, is that of the therapeutic addict. In a series of one hundred cases referred to the Ministry of Health through the Home Office, 55 per cent were found to be over 60 years old. Thirty-five per cent had been on the drug for three years, 35 per cent for six years and 30 per cent for more than six years. Eighty per cent were started on their drug by their general practitioner, 10 per cent by a consultant and 10 per cent of their own accord. In 75 per cent of these cases there were good medical grounds for starting and continuing the drug. There is no 'registration scheme' for addicts in this country; most are known to the Home Office and the Ministry of Health, but remain under the care of their own doctors. The fear of dangerous drugs in this country is such that useful, if dangerous, analgesics are sometimes withheld when they should be given.

Dr Isbell began by pointing out that drug addiction in the United States is a small problem compared to others such as alcoholism and tuberculosis. Nevertheless it is much greater than in Great Britain. The reasons for this may be :

Climatic and historical. In the southern, almost subtropical parts of the United States there used to be a high incidence of infectious diarrhœal disease which could not be treated. The only source of symptomatic relief was with opiates and with the chronic

nature of the disease and the poor living conditions, many people became innocently addicted.

Civil war. Many of the casualties became addicted as the dangers of morphine were not realised. Addiction was so common in veterans as to be known as the 'Soldiers Disease'.

Importation of Chinese labourers to Western America. They brought with them their national practice of smoking opium and by 1890 the United States was second only to China as an importer of smoking opium.

Thus the United States had a problem arising from peculiar circumstances which did not exist in Europe.

Some 40,000 people are at present in conflict with the law on account of narcotics. Therapeutic and professional addicts do exist, but they are few in proportion to the delinquent type. The problem is sharply localised in certain areas of the cities of New York, Chicago, Washington and Los Angeles characterised by low incomes, unstable families and minority groups. Psychiatrically, delinquent addicts have personality disorders and live in bad surroundings. They seem unable to learn from experience or to exert self-control. They are very similar in all ways to delinquents of other sorts.

Pharmacologically, there is evidence that addiction is both a mental and a physical state.

In introducing the third member of the panel, Dr M. Nimb, *Professor Dunlop* commented on the fact that Denmark, which is a highly developed Welfare State, seems to have a far greater problem of drug addiction and suicide than countries such as Spain and Italy where poverty is rife.

Dr Nimb referred to the ketobemidone combination about which Dr Petersen had spoken. In the total picture of addiction in Copenhagen this preparation appears to play a very insignificant role among the substances used by drug addicts.

The problem of drug addiction had, he felt, many facets. The psycho-pharmacological methods of Isbell and his colleagues could now be applied so accurately to the study of a new drug that the disastrous mistakes of the past would not happen again. But the drugs were not the only factor; addiction was a public health problem, a problem of international trade and control, of the management of criminals, of social and human unhappiness.

Finally, it was important that physicians and general practitioners should show equal caution with all drugs of addiction. There was a fairly widespread idea that methadone was a little safer than morphine; perhaps because of this, methadone was the drug most widely used by addicts in Copenhagen.

Dr Stern asked Dr Isbell about laboratory addiction produced in

animals; monkeys seemed to react more strongly to pethidine-type compounds than, for instance, to methadone, which was not so in man.

Dr Isbell agreed, but said that no reason had yet been found for this; perhaps it was due to differences in metabolism. The final test must still be in man.

Dr H. C. Churchill-Davidson (London) asked that addiction might be put in its correct perspective. He felt that nursing staff were so afraid of using addicting drugs that patients did not receive them as often as they should. How easy was it to make an addict out of a normal person?

Dr Isbell answered that it depends on what is meant by addiction. If only physical dependence is meant, then *all* people would become addicted in the sense that they would have symptoms of abstinence when the drug was withdrawn, if they received it for a long enough period. But physical dependence is only one aspect of drug addiction and it is difficult to say what proportion of these people would become true addicts. If they did not know what the drug was, practically none of them would become addicted. If, however, the administration of the drug was in their own hands, several people out of, say, 100 might become addicted.

Dr Peter Nathan (Medical Research Council) said that among ninety patients suffering from cancer and treated by pain-relieving operations, many had been receiving morphine or methadone for prolonged periods. None of these demanded the drugs after their pain had been relieved. No withdrawal symptoms had been observed, but these might have been missed in the immediate post-operative period.

Dr Nathan was convinced that because of the fear of addiction, many patients, in hospital and elsewhere, suffer pain which could be relieved by enough of an analgesic drug.

We are indebted to the Society of Chemical Industry for their courtesy in enabling us to summarize the Lister Memorial Lecture which was published in *Chemistry and Industry*, 21st November, 1959; and to Messrs Duncan, Flockhart & Co., Ltd., for the summary of the symposium on Analgesia. [Editor, *Anæsthesia*.]

NEW INVENTIONS

Unless expressly stated by the authors no claim to originality or priority is made and items given under this head include modifications to existing apparatus. The Editor regrets that space considerations make it impossible to publish correspondence on this subject

Electro-sphygmophone

A new pulse detector

G. C. TANDAN and R. S. THAPAR

This is an electronic remote control multi-channel instrument, working on the familiar principle of pulse detectors that pick up, amplify and record on a meter the arterial or capillary pulsation, with the modification that in addition to visual recording of such activity, sonic signals are produced through high gain amplifiers. In addition an electronic sonic and visual time signal circuit is incorporated so that a neon flash and sonic signal of distinct character is produced. The timer control can vary the signal interval between two flashes to three or six seconds. By counting the sonic pulse signals between two sonic time signals and multiplying by time factor of timer selector switch, pulse rate can be directly obtained without reference to watch or distraction.

A sound volume compressor is incorporated to eliminate stray noises. By use of a cuff and manometer, systolic and diastolic blood pressures can be recorded remotely through long rubber tubes by noting the return of first pulse sounds at systolic BP level, and frictional sounds at diastolic BP level.

The instrument is provided with multiple circuits so that more than one patient can be monitored by a patient selector switch. A lead with a special microphone can be attached to the patient's neck for listening to respiration or laryngeal secretions. In a recovery room four to five patients can be monitored from the nurse's table with a single multi-channel sphygmophone. The instrument is in two parts. One part connected to the patient is powered by a long life 1.5 volt dry cell and can function independent of a.c. mains, giving visual indication of pulse on the meter. This carries no hazard of explosion due to inflammable atmosphere.

The timer, compressor and loud speaker circuits powered by a.c. mains comprise the other half and are housed in a separate case. This is connected to the pulse unit by long leads and located remotely to eliminate high voltage hazards. The signals are self-imposing, and faithfully reproduce the pulse wave form.

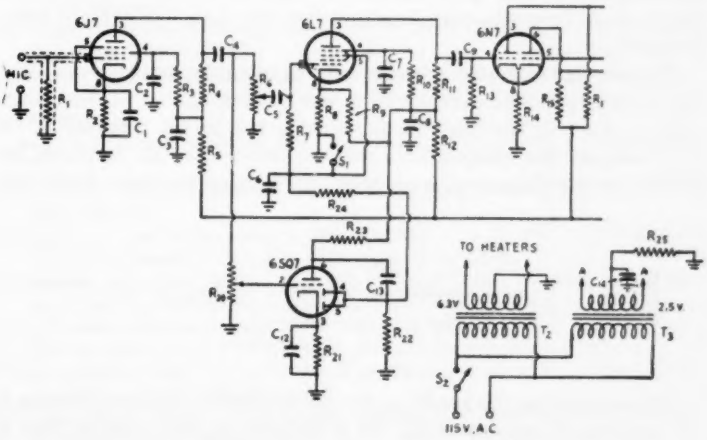


FIG. 1 Circuit of electro-sphygmophone.

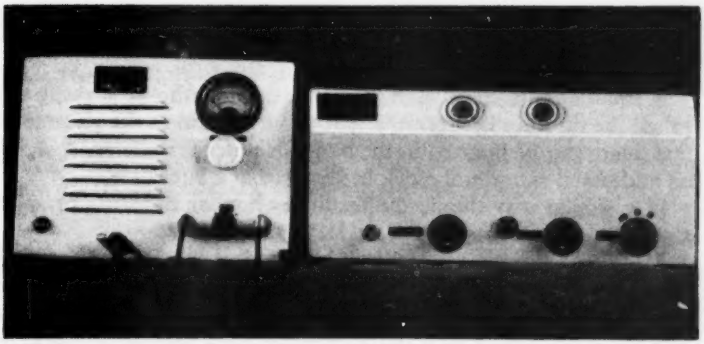


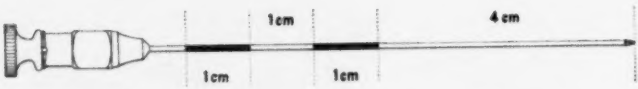
FIG. 2 Electro-sphygmophone with 2 channels.

Specially marked needle to facilitate extradural block

J. ALFRED LEE

One of the difficulties associated with the successful insertion of a needle point into the extradural space is to know how deeply placed the needle is at any given time. The distance from the skin to the space varies from less than 3cm to more than 6cm, the average being about 4½cms.

The needle illustrated has alternate black and metallic zones, each measuring 1cm. The distance from the needle point to the first black zone is 4cm. It has been in day to day use in the theatres of the Southend-on-Sea Hospitals for the past two-and-a-half years and has proved very satisfactory in reducing our incidence of dural punctures.



When inserting the needle in the lumbar region, one can advance it, in patients of average build, for a distance of 3cm without fear of missing the extradural space or of puncturing the dura and this distance can be readily calculated from the fact that the first black zone is still 1cm away from the skin surface. From this point onwards, care must be taken. Similarly, if the extradural space has not been located when the point has been inserted 6cm, one is, in all but the most robust and big boned patients, in tiger country, from which it may well be discrete to withdraw and try again at a different angle, or from another interspace.

A small additional advantage is that the anæsthetist is easily able to tell the distance between the space and the skin at the given level; this figure can be inserted in the patient's notes for reference, should an additional extradural block be required at a later date.

In a similar way the needle facilitates lumbar puncture or spinal analgesia.

Mr Childerhouse of Medical and Industrial Equipment Ltd., 10 – 12 New Cavendish Street, London W1 has kindly provided the figures. He is able to supply the Howard Jones, Tuohy, or any other type of spinal needle with the alternating black and silver markings.

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Book Reviews

XYLOCAINE

THE PHARMACOLOGICAL BASIS OF ITS CLINICAL USE

STEN WIEDLING

Pp. 146. Figs 24. Almqvist & Wiksells. Stockholm. Price Sw. kr. 20.

It is probable that lignocaine (proprietory name xylocaine) is the most widely used local analgesic at the present time. Dr Wiedling of the Research Laboratories of AB ASTRA, Sweden, has produced an excellent monograph of the experimental chemical and pharmacological work which has been carried out in connection with this drug. The result is a most useful reference book, but it should be noted that no details are given of any techniques of local analgesia. The small volume is well produced and has a foreword by Dr Torsten Gordh who did much of the pioneer work with lignocaine. A comprehensive bibliography and index of authors and drugs conclude the book.

A PRACTICE OF ANÆSTHESIA

W. D. WYLIE and H. C. CHURCHILL-DAVIDSON

Pp. xv + 1056. Figs. 246. Lloyd-Luke (Medical Books) Ltd. London. Price 105s.

The practice of anæsthesia now has so many aspects and ramifications that most modern authors have not even tried to cover the whole of it. Consequently most of the books on anæsthesia available in this country are either monographs dealing with one particular subject or are summaries or 'cram books' designed mainly to help candidates for the higher examinations. Drs Wylie and Churchill-Davidson have boldly set out to compass the whole field of anæsthesia and analgesia in the light of present day knowledge and have done so by the novel method of considering the various systems of the body in six sections. This formidable task could only have been accomplished by assuming that readers already possessed a knowledge of elementary anæsthesia. Consequently we find that most actual techniques are referred to rather than described and the emphasis is laid on the reasons for their adoption. It is clear that an immense amount of work has been expended in the preparation of this book. It is difficult to find omissions and repetition has been almost eliminated. One is impressed by the restraint in style and the frank admission of incomplete knowledge when proofs are lacking. For example, 'the problem of the possible dangers of hyperventilation during anæsthesia has as yet been inadequately investigated but it is obviously of importance'. As would be expected, the section on myoneural b'ock is outstandingly good.

Dr M. D. Nosworthy has written a foreword and the following contributors have given their views on special subjects:

Dr T. H. S. Burns on Fires and Explosions.

Dr C. A. Foster on Traumatic Injuries, Burns, the Electroencephalograph, Sedative, Hypnotic, Antihistamine and Tranquillizer Drugs.

Dr M. S. R. Hutt on Blood Transfusion.

Dr J. D. Laycock on The Treatment of Pain and the Analgesic Drugs.

Dr D. D. B. Morris on Local Analgesic Drugs and Spinal and Epidural Analgesia.

Mr K. E. D. Shuttleworth on Surgical Shock and Water and Electrolyte Replacement.

Dr R. B. Wright on Anæsthesia and Cardiac Disease.

All these writers, with one exception, are on the active staff of St Thomas's Hospital and the book as a whole can be regarded as representing current anæsthetic practice at that institution. It is undoubtedly a notable addition to the literature. Each chapter ends with an alphabetical list of references and there is a fairly comprehensive index. An appendix on the care and sterilization of instruments and a 'vade-mecum' are included. The printing, illustrations, paper and binding are all first class and typographical errors are rare.

To a young anæsthetist, five guineas represents a considerable sum, but if he spends it on this book it can hardly fail to prove a sound investment.

GENERAL ANÆSTHESIA

Edited by

FRANKIS T. EVANS and T. CECIL GRAY

2 Volumes: £7.7.0 per set. Butterworth, London, 1959

'General Anæsthesia' succeeds and surpasses 'Modern Practice in Anæsthesia'. The editors state their aim to produce a book suitable for both study and reference and as comprehensive as it is practicable to make it. As the title implies, detailed consideration of local analgesia has been omitted. In this task thirty-nine British contributors have succeeded in filling forty-six chapters occupying 962 pages of text. Thus this is a substantial addition to the stream of anæsthetic literature which is at present in full spate.

The first volume takes in basic principles covering those specialised aspects of anatomy, physiology and neurophysiology which are of importance to anæsthetists in their everyday work, together with pre-anæsthetic considerations, some pharmacology, transfusion and fluid and electrolyte balance. Techniques, special fields and hazards are detailed in the second volume, where the anæsthetic approach to various types of operation is discussed.

In view of the size of the team a surprisingly high overall standard has been attained. The book is well produced, but the diagrams are sometimes inadequate in number and in scale; for the price one might expect a more generous standard of illustration.

After most chapters an ample and up-to-date bibliography is cited, and there are only a few topics upon which one might chase information without finding at least a pointer.

Some chapters are outstandingly good, among them those on the relaxants, on anæsthesia in abdominal surgery, on water and electrolyte balance and on the role of the anæsthetist in respiratory insufficiency. The section on methods of measurement in anæsthesia is a valuable innovation which one hopes may be expanded in a future edition. The extensive chapter on physiology of the nervous system presents much information that is not readily accessible to anæsthetists. In the important chapter on respiratory physiology the discussion of several topics is disappointing, in particular the section on respiratory dead space could be improved. In the chapter on anatomy one appreciates that only a limited treatment was intended, but the anatomy of the lungs and tracheo-bronchial tree

is of such importance to anæsthetists that a fuller account and more ample diagrams might have been expected. Although anæsthetics for dental and ophthalmic operations are covered, it seems a pity that there is not a chapter on anæsthesia for ENT surgery, for discussion of several important topics has thus been omitted.

The number of misprints is very small, among them must surely be the suggested dosage of d-tubocurarine chloride as 2.5 – 3mg per kg (p.432 Vol. 1) and the 5 per cent solution of sucrose advocated for treatment of cerebral œdema (p.375 Vol. 2); there is no doubt a similar explanation for the tidal volume of 50ml tabulated on p.56 Vol. 1.

Despite these criticisms the editors have been notably successful in their aims, especially in keeping the book right up-to-date: therefore, this work will appeal to all those striving to keep up with the enormous advances recently made in anæsthesia.

Obituaries

Dr Reginald William Ironside, consulting anæsthetist to the West London and Royal Masonic Hospitals, died on 20 September 1959, at the age of 78. The son of a Hampstead practitioner he was educated at Pembroke College, Cambridge and at Westminster Hospital, qualifying in 1906. His studies had been interrupted by service with the Royal Fusiliers for which in 1902 he was awarded the South African War medal. After house appointments at the Westminster and Great Ormond Street Hospitals he combined general practice in South Kensington with a physicianship at Queen Mary's Hospital for the East End. During the first World War he was in France first with the 10th Hussars as medical officer and later in command of a Casualty Clearing station. In the inter-war years he turned his attention to the specialty of anæsthetics and was appointed to the staffs of the West London and Royal Masonic Hospitals. He acquired the DA in 1935 and became a Fellow of the Faculty in 1949. He was a Fellow of the Association, having joined it in 1948.

'Reggie' Ironside was one of the last of those stalwarts who successfully combined the specialty of anæsthetics with general practice and his death will come as sad news to a great number of colleagues and old patients.

G.E.

The death of **Dr Raymond Apperly** in his seventy-seventh year removes from the world of anæsthesia one of the veritable veterans of our tide of time.

A severe attack of coronary thrombosis in 1943, not the first evidence of cardiac derangement, together with almost contemporaneous damage to his London home from enemy bombardment, sent him down to his native Gloucestershire and he was but rarely seen in London again. From his beloved hills and dales that surround the Stroud valley, where he enjoyed tolerable health for a time, he removed to Worcestershire for family reasons where a more definite evidence of serious cardiac insufficiency began to manifest itself and he died in Evesham hospital.

It was natural that he should have joined Middlesex Hospital as a student since many of his family had been there before him and his father had entered 'Middlesex' as a dental student in 1864. Raymond held the usual house appointments: he rapidly shewed himself to be a most excellent clinician: more than half a century ago he made the first pre-operative diagnosis of acute pancreatitis in 'Middlesex', for which statement I can vouch as the operating surgeon! He was house-physician to William Pasteur, at a time when the latter was interesting himself in the problem of pulmonary collapse, especially after operations: it was not unnatural that one who had won the Lyell Gold Medal and Scholarship in Surgery should turn his thoughts towards a house-surgeoncy, and fortune happily led to his association with Bland-Sutton, a parnership between surgeon and anæsthetist that was to develop into a deep friendship to endure as long as 'J.B.S.' lived. It was Bland-Sutton who persuaded Apperly to relinquish the thought of general practice towards which he had already taken the first step.

From that moment I doubt whether Bland-Sutton ever performed an operation without the collaboration of his loyal colleague and friend – Apperly worshipped Bland-Sutton! Professional competence secured a demand for Apperly's services by surgeons of London hospitals apart from 'Middlesex' – Trotter, Lane, Bromley of Guys, Sydney Macdonald, William Gilliatt, Elphick, Robert Jones when on London visits, Anderson Critchett, Clifford Morson and many others. His experience was a mirror of London surgical practice up to the outbreak of the second world war.

Apperly was in no sense an investigator but a consummate artist with the vehicles of anæsthesia available in his time. He was particularly expert in the use of chloroform and was at his very best in its employment for such operations as those for cancer of the breast, tongue, pharynx, larynx, etc.; I doubt if he had ever had a death from chloroform. He was also a master of the art of regional analgesia and took the trouble to journey to Vienna, Innsbruck and Zurich to improve himself in the technique. He must have been the first anæsthetist in Britain to produce splanchnic analgesia by the posterior route and for some years we employed this for gastric operations until our adoption of the anterior and more accurate method. The wheels of time roll on and this epoch in anæsthesia is but history to-day, but Finsterer made a definite contribution towards greatly reducing, even to a microscopic figure, the mortality of gastric operations that had been so largely related to the inhalation methods of anæsthesia of that time.

Apperly must have been one of the very first anæsthetists to visit pre-operatively the patient whom he was to anæsthetize on the morrow, and this had been his invariable habit in and out of hospital from the first day he became a professional anæsthetist in the first decade of the century. He was, perhaps, fortunate in the particular period of his professional activity: the rapid operating of Bland-Sutton and the surgeons of that generation suited his restless eager temperament: he became 'bored' with a gastrectomy that occupied much more than fifty minutes: he would have been absolutely intolerant of the lengthy operations of to-day.

Although he may not have been an investigator, Apperly was keenly alive to all the advances in anæsthesia and belonged to a small private club of anæsthetists of whom Sir Francis Shipway must now be the sole survivor. Despite the pain of a hip joint and the restricted physical activity imposed on him by his cardiac condition, he retained his sunny disposition. His marriage was an intensely happy one: in the words of Horace, 'For nothing is greater or better than this, when man and wife dwell in the house in harmony, a joy to their friends, but they know this best themselves'; Raymond and 'Peg's' golden wedding anniversary was only a month or two ago.

The mention of Apperly's name at once conjures up the memory of Bland-Sutton and it is a source of regret that he never wrote the story of his hero. He must have known 'J.B.S.' better than anyone and many of the Bland-Sutton tales have come from 'R.E.A.' In those days of peripatetic surgery, I, too, travelled miles with him: he knew every good inn within a hundred miles of London for he

loved good food and was a connoisseur of wine. Our many journeys together revealed to me his well-stocked mind for he was a lover of good literature: above all he was a great Churchman.

His outstanding qualities were directed to the best interests of his patients and the most loyal devotion to his colleagues and pupils and to all those for whom and with whom he worked.

GORDON GORDON-TAYLOR

We much regret to report the death of **Dr Gilbert Brown** at Adelaide, South Australia at the age of 77. Dr Brown graduated MB, ChB in 1908 at the University of Liverpool. In 1912 he emigrated to Australia and went into general practice, at first in Snowtown and then in Gilberton. In the first world war he was in charge of a quarantine station in West Australia. In 1920 he took up anæsthetics and was made a specialist to the plastic surgery unit of the Keswick Repatriation Hospital and to the Adelaide Children's Hospital. In the following year he was appointed to the Royal Adelaide Hospital and became instructor in anæsthetics at the medical school. He took the DA in 1935 and became FFARCS in 1950. During the second world war, he worked at No. 105 Military Hospital and was decorated with the CBE in 1953. Dr Gilbert Brown was a pioneer of modern anæsthesia in Australia and was the first president of the Australian Society of Anæsthetists. His fine work was recognized in this country and in 1935 he was elected an honorary member of the Liverpool Anæsthetic Society.

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ANÆSTHESIA FOR FREDET-RAMMSTEDT'S OPERATION

The Editor, *Anæsthesia*

Sir,

We would like to thank Drs Black and Love for their comments on 'Anæsthesia for Fredet-Rammstedt's Operation'. We agree that it is possible to intubate healthy infants whose weight is in excess of seven pounds and that this is a purely arbitrary figure. In heavier infants, however, the amount of force necessary to visualise the glottis may cause some degree of trauma, especially if expert assistance is not available.

It is true that occasionally some difficulty may be encountered in inflating apnœic infants. In our experience this has always been overcome by inflating gently and if necessary by inserting a miniature Guedel's airway.

Perhaps we have been fortunate in this respect and also in that we have not seen regurgitation following the use of suxamethonium unless it was associated with surgical manipulation of the stomach.

It is interesting to hear that Dr Love is using the technique of intubating the conscious infant, inducing anæsthesia with nitrous oxide–oxygen and relaxation with intramuscular or intravenous suxamethonium. We wonder how his experiences with this technique compare with our own. We have heard good reports regarding induction of anæsthesia with halothane but have no personal experience of this technique.

Yours faithfully,
H. I. A. Nisbet
F. Wilson
A. J. Booth

HALOTHANE AND HYPOTENSION

The Editor, *Anæsthesia*

Sir,

I have read with interest Dr Enderby's article on halothane and hypotension in the January issue of the Journal.

When halothane was first introduced to clinical practice, I was careful only to use it in a semi-closed circuit and then in a concentration not exceeding 2 per cent. If this, when aided by posture, did not give me the hypotension I required, I supplemented it with either a trimetaphan or a phenactropinium drip. This supplementation, however, was often associated with a increase in pulse rate and I have grown to dislike the combination of tachycardia and hypotension, for an added strain is placed upon the heart and the incidence of ECG changes is significantly increased.

I accordingly decided, some two years ago, to omit the ganglion blockers and employ halothane in a concentration in excess of 2 per cent until I obtained the requisite degree of hypotension (usually 60-70mm Hg at heart level). Controlled

respiration with hyperventilation, using a 3 litre flow (50 per cent nitrous oxide-oxygen) through a closed circuit and an endotracheal tube was employed, so that adequate oxygenation and carbon dioxide elimination were ensured.

Provided constant attention is paid to the pulse rate and blood pressure and the concentration of halothane is titrated to these, I see no need to employ ganglionic blocking drugs in addition.

In my view, halothane has made hypotensive anæsthesia both simple and safe, but it should be stressed that safety in anæsthesia is not so much the property of an agent or technique, as a virtue of the administrator; eternal vigilance is the price of liberty.

Yours faithfully,
W. N. Rollason

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References: Treatment of Cardiac Shock by Metaraminol.
Brit. med. J., 1959, **1**, 1081.

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Association News

We congratulate Dr Vernon Hall on the honour of being asked to attend H. M. The Queen on the recent happy occasion of the birth of a Prince and also on his appointment to Commander of the Royal Victorian Order.

We heartily congratulate **Sir Ivan Magill** on receiving the KCVO in the New Year Honours.

The Annual Meeting of the Association will be held on 4 – 5 November 1960 at the Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2.

The Annual General Meeting will be held during the afternoon of Friday 4 November, followed by the third John Snow Memorial Lecture. The Annual Dinner will be held at the Royal College of Surgeons in the evening.

Scientific papers will be read on Friday and Saturday morning. Those wishing to read a paper are asked to submit a summary of about 200 words to the Honorary Secretary *not later than 31 May 1960*, for the consideration of the Programme Committee.

In 1961 the Annual Meeting will be held in Dublin from 18 – 21 October.

The Council of the Association wishes to remind Fellows and Members of the importance of subscribing to the **Hospital Medical Staffs Defence Trust Fund.** Heavy expenses are being incurred in various directions *e.g.* in the test cases to establish for part-time consultants the right to be assessed for income tax under Schedule D and not Schedule E. Subscriptions should be sent direct to the Secretary of the Trust, Dr S. J. Hadfield at B M A House, Tavistock Square, London WC1.

The third international **Conference on Medical Electronics** is being held at Olympia, London from 21 – 27 July 1960. It is being organized by the Electronics and Communications Section of the Institution of Electrical Engineers and the proceedings should include many items of interest to anæsthetists.

Five day intensive **courses in dental anæsthesia** will be held at the Eastman Dental Hospital between 4–8 April, 18–22 July, 10–14 October and 19–23 December 1960, during which ten lectures are given and there are ten out-patient anæsthetic clinics, as well as a minimum of two operating sessions for major oral surgery.

Each postgraduate is given the opportunity of giving anæsthetics under supervision, both to children and adults in the Out-patient Department.

Further particulars can be obtained from The Dean's Secretary, Institute of Dental Surgery, Eastman Dental Hospital, London WC1.

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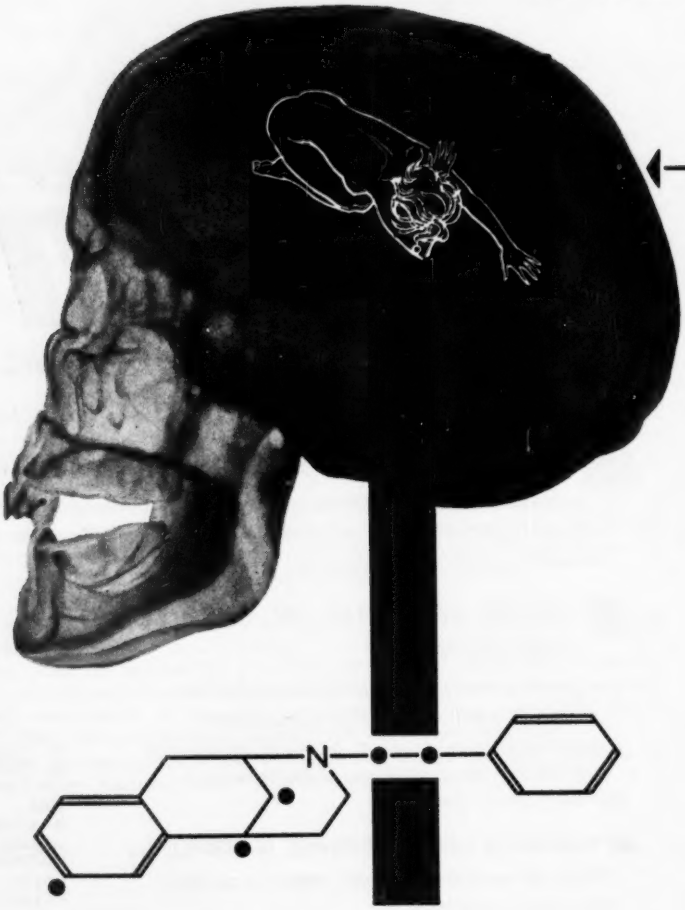

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Commonwealth and Foreign News

The **Society of Anæsthetists of Hong Kong** held a meeting on 13 November 1959 at which Professor Sir Robert Macintosh read a paper on 'Anæsthetics used in Research'. Sir Robert has been making an extensive tour of the Far East including Russia, China, Japan and the Philippines.

The first **McDermott Visiting Professorship in Anesthesiology** has been awarded to Dr D. A. Buxton Hopkin of Charing Cross Hospital. The appointment is for one year starting in April 1960 and tenable at the South-western Medical School at Dallas, University of Texas, U.S.A.

The **Netherlands Society of Anæsthetists** has elected the following officers for 1960: B. de Vries Robles, President (Diepenbrockstraat 24, Amsterdam); Dr J. F. Crul, Secretary (Sterreschansweg 40, Nijmegen); J. van 't Oever, Treasurer (63 Ringdijk, Rotterdam); G. P. W. van Waasbergen, Member; L. D. J. Reeser, Member.

The sixth **Brazilian Congress of Anæsthesia**, was held in Belo Horizonte, from 18 – 24 October 1959.

Attendance was estimated at 170 members, out of 500 in the whole country. Diplomas were granted to those who passed examinations for the EASBA title and also to Drs Pena and Souza Meta, as pioneers in the specialty. Chosen subjects of the Congress were grouped around the two main ones, that is, 'Cardiac Arrest' and 'Intravenous Barbiturate Narcosis'. Panel discussions were held on 'Nitrous-oxide', 'Non-rebreathing techniques' and 'Extracorporeal circulation'. Honour guest from the USA was Dr Douglas Eastwood, from Virginia, who showed an electronic monitor of the pulse rate. Lectures were also given on 'Carbon dioxide and anæsthesia', and 'Anæsthesia and plastic surgery'. The general aspects of this meeting suggest that the Brazilian Association is flourishing and that maturity is keeping pace with blooming.

The officers of the **Israel Society of Anesthesiologists** for 1960 are:

CHAIRMAN Dr M. Chayen

HONORARY SECRETARY–TREASURER Dr D. Backner

The address of the Secretariat is 3 Emden Street, Tel Aviv, Israel. Seven major meetings were held at various hospitals during the past year. Overseas guests included Dr W. D. Wylie, Dr P. Edwards and Dr S. Shane.

REVISED SUGGESTIONS TO CONTRIBUTORS

Original articles, 'New Inventions' etc. are accepted for publication on the understanding that they are contributed exclusively to '*Anæsthesia*', and become the property of the Association of Anæsthetists. Articles are subject to such alterations as the editor may deem necessary, but no major alterations will be made without the author's consent. After publication, the editor will be pleased to consider requests by authors to borrow and use any blocks made to illustrate their articles.

PREPARATION OF ARTICLES

Articles should be typewritten on one side of the paper only, and should be double spaced. Margins of 1½" should be left on both sides of the typescript. Corrections should be made in ink, and should be legibly written. The first sheet of the article should contain only the following details: title of the article; the author's name and the higher of his degrees and diplomas; his present or immediate past appointment; the address to which proofs of the article should be sent.

TITLES OF ARTICLES should be restricted to five words. If this is impossible, a subsidiary title of not more than twelve words can be inserted. A more detailed description of the scope of the article can be given in the first paragraph of the text.

HEADINGS IN THE TEXT are useful to 'signpost' the arguments elaborated in the article. They should be brief and clearly defined in the typescript. Main headings should be typed in capitals, and subsidiary headings to these main headings should be typed in small letters and underlined. No heading should appear in the text until after the first or second paragraph. Too many headings are better than too few. The numbering of headings and paragraphs is not recommended.

THE USE OF FIGURES in articles should be watched carefully. Where statistics are given in the text of the article, figures should be used; likewise the measurements of drugs should be given in figures. But phrases such as 'After three days', 'ten minutes later' etc. should be given in words.

DRUG NAMES AND MEASUREMENTS. The established practice is to use the BPC Approved Name for all drugs and not the chemical or trade name. The only exceptions are when a drug has not been named by the BPC in time for publication, and in the case of certain unusual drugs, the trade name may be given in parenthesis after the approved name, *e.g.* hyoscyamine (bellafoline). The dose of drugs etc. should be given in metric quantities, except for those drugs which are commonly prescribed in avoirdupois measures. In the latter case, the metric equivalent should be given in parenthesis.

REFERENCES to the literature should be clearly indicated in the text by superior figures(⁹), and should be set out fully in numerical order on the following system: LANGLEY, J. N. (1919). *J. Physiol., 53, May,* 120. The list of references should form the last sheets of the article.

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Faculty News

Election to the Board. At the Election to the Board held, after a postal ballot, on 9 March, the following Fellows in the Faculty were elected to the vacancies occasioned by the death of Mr Bernard Johnson and the retirement in rotation of Dr W. A. Low, MC, Dr M. D. Nosworthy and Professor E. A. Pask, OBE:

Dr M. D. Nosworthy (re-elected).
Dr J. Alfred Lee.
Dr G. Jackson Rees.
Dr W. D. Wylie.

Dr R. V. Sturton was elected to the vacancy occasioned by the resignation of Dr H. C. Churchill-Davidson to represent the Members of the Faculty.

Honorary Fellowship in the Faculty of Anæsthetists. The Council of the Royal College of Surgeons of England, on the recommendation of the Board of Faculty, has elected Sir Henry Dale, OM, GBE, FRCP, Hon. FRCS, FRS, Chairman of The Wellcome Trust, and Mr Archibald Marston, CBE, FRCS, FFARCS, to the Honorary Fellowship in the Faculty of Anæsthetists. Mr Marston was the first Dean of the Faculty.

Scientific Meeting. A one-day symposium on 'Hypoxia', of which particulars may be obtained from the Secretary of the Faculty, will take place at the Royal College of Surgeons on Saturday 7 May.

Anæsthetics Course. The next intensive course of lectures, demonstrations and tutorials in anæsthetics will be held at the Royal College of Surgeons from 7 – 17 June.

Frederic Hewitt Lecture. The Board of Faculty has elected Dr R. P. W. Shackleton, FFARCS as Frederic Hewitt Lecturer for 1961.

Primary FFARCS Overseas. A Primary FFARCS examination was held in Colombo in January, the first time that this examination has taken place outside London. Of the five candidates who presented themselves two were successful. The examiners were Professor E. A. Pask (Pharmacology), Professor D. V. Davies (Anatomy), Professor R. Knox (Pathology) and Professor A. C. E. Koch, of the University of Ceylon (Physiology).

FFARCS Examination. At its meeting on 11 February the Council of the Royal College of Surgeons approved the award of the Diploma of Fellow in the Faculty of Anæsthetists to the following successful candidates at the examination held in January:

DODD, KEITH WILLIAM
BURCHELL, GEOFFREY BARNETT
BROWN, IAN MICHAEL
HARDY, THOMAS KENNETH
EVE, NORMAN HOWARD
MILNE, MALCOLM ROSS
BRAUDE, WILLIAM
DYKES, WILLIAM STEWART
DAVIDSON, IAN WALTON
UMRIGAR, SOHRAB RUSTOMJI
DAVIE, ROBERT DUNCAN MCCALLUM
JAFRY, NASIR HUSAIN
MCCORMICK, PETER WILLIAM
WEST, MARY FRANCES
ADAM, CATHERINE KENNEDY
CLARKE, GORDON

THORPE, JAMES NOEL
SIMPSON, MARIE MARGARET
COLBECK, WILLIAM JOHN
ELESH, WINIFRED ELVA
ELLIOTT, CHRISTOPHER JOHN RICHARD
HICKS, JOHN PETER NEVILLE
LODGE, ALAN BLAKEY
MCCLEERY, WILLIAM NOEL COLVAN
MCLEOD, NORMAN
MOIR, DONALD DUNDAS
ROSS, EDWARD DANIEL TUE
TSOI-A-SUE, PATRICK ALEXANDER
DAVIES, DAVID MERVYN
FISK, GRAHAM CHUDLEIGH
HARRIS, DOROTHY EILEEN
MCCLEMENTS, DAVID TEMPLETON
HART, DAVID DRUMMOND
KNELL, PATRICK JOHN WARREN
MAIR, IAN MICHAEL JAQUES
MANNING, ROBERT ROSS
SPEIRS, ISOBEL
WIJEYARATNE, LAKSHMAN TISSE
CLARKE, FREDERICK BRIAN NORTON
FULLER, ANDREW THOMAS RADBURNE
HIDER, CALVIN FRASER
LYDER, BRIAN ASHBY
MAUNG U WIN
STEVENS, JOHN HENRY
TAYLOR, THOMAS HENRY
THOMSON, RICHARD JAMES GRAHAM

The President, Vice-President and Council of the **Royal College of Surgeons in Ireland** have instituted a Faculty of Anæsthetists and have elected the following to the first Board of Faculty:

DEAN	Dr T. J. Gilmartin.
VICE-DEAN	Dr V. O. McCormick.
COUNCIL REPRESENTATIVE	Mr D. J. Riordan.
	Dr P. Drury-Byrne.
	Dr R. Davys.
	Dr J. W. Dundee.
	Dr S. Kenny.
	Dr H. Love.
	Dr P. Murray.
	Dr P. Nagle.
	Dr J. A. Woodcock.
EX-OFFICIO	Mr T. G. Wilson, President of the Royal College of Surgeons in Ireland
	Mr S. Heatley, Vice-President of the Royal College of Surgeons in Ireland

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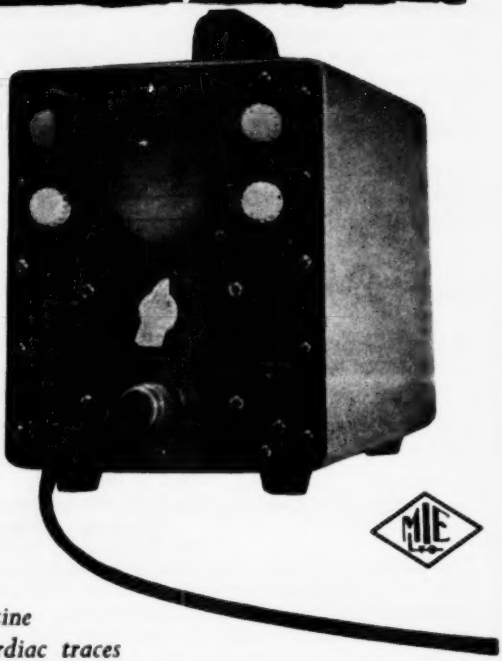

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